GuLF Worker Study:

Gulf Long-Term Follow-Up Study for Oil Spill Clean-Up Workers and Volunteers

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Table of Contents

List of Abbreviations

AE	Adverse event
AAPOR	American Association for Public Opinion Research
BFR	Brominated flame retardant
BISCO	Bayou Interfaith Shared Community Organizing
BP	British Petroleum
BPSOS	Boat People SOS
CAG	Community Advisory Group
CAI	Computer-Assisted Interview
CATI	Computer-Assisted Telephone Interview
CBC	Complete blood count
CLSI	Clinical Laboratory Standard Institute
CS	Clinical specialist
DMS	Data management system
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GCF	Gulf Coast Fund
GCP	Good Clinical Practices
HVA	Home Visit Agent
IRB	Institutional Review Board
JEM	Job-exposure matrix
LFT	Liver function test
MQVN CDC	Mary Queen of Vietnam Community Development Corporation
NAGs	N-acetyl-beta-D-glucosaminidase
NGAL	Neutrophil gelatinase-associated lipocalin
NGO	Non-governmental organization
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
PAH	Polycyclic aromatic hydrocarbon
PEC	Petroleum Education Council
PTSD	Post traumatic stress syndrome
RFP	Request for proposal
VOC	Volatile organic compound
WBC	White blood cells

Protocol Summary

Full Title:	Gulf Long-Term Follow-Up Study for Oil Spill Clean-Up Workers and Volunteers
Short Title:	GuLF Worker Study
Conducted by:	NIEHS and SRA (NIEHS Epidemiology Branch Clinical Research Contractor)
Principal Investigator:	Dale Sandler, Ph.D. Division of Intramural Research Epidemiology Branch National Institute of Environmental Health Sciences
Sample Size:	55,000
Study Population:	Workers and volunteers engaged or potentially engaged in oil spill clean-up operations in the Gulf of Mexico
Accrual Period:	10/2010 – 4/2012
Study Design:	Closed prospective cohort
Study Duration:	10 years initially, with the possibility of extending the follow-up period
Primary Objective:	To investigate potential short- and long-term health effects associated with oil spill clean-up activities/exposures surrounding the Deepwater Horizon disaster
Secondary Objectives:	To create a resource for additional collaborative research on focused hypotheses or subgroups
Exploratory Objectives:	To investigate biomarkers of potentially adverse biological effect in relation to oil spill clean-up activities/exposures
Endpoints:	Respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, hepatic, and renal effects

Précis

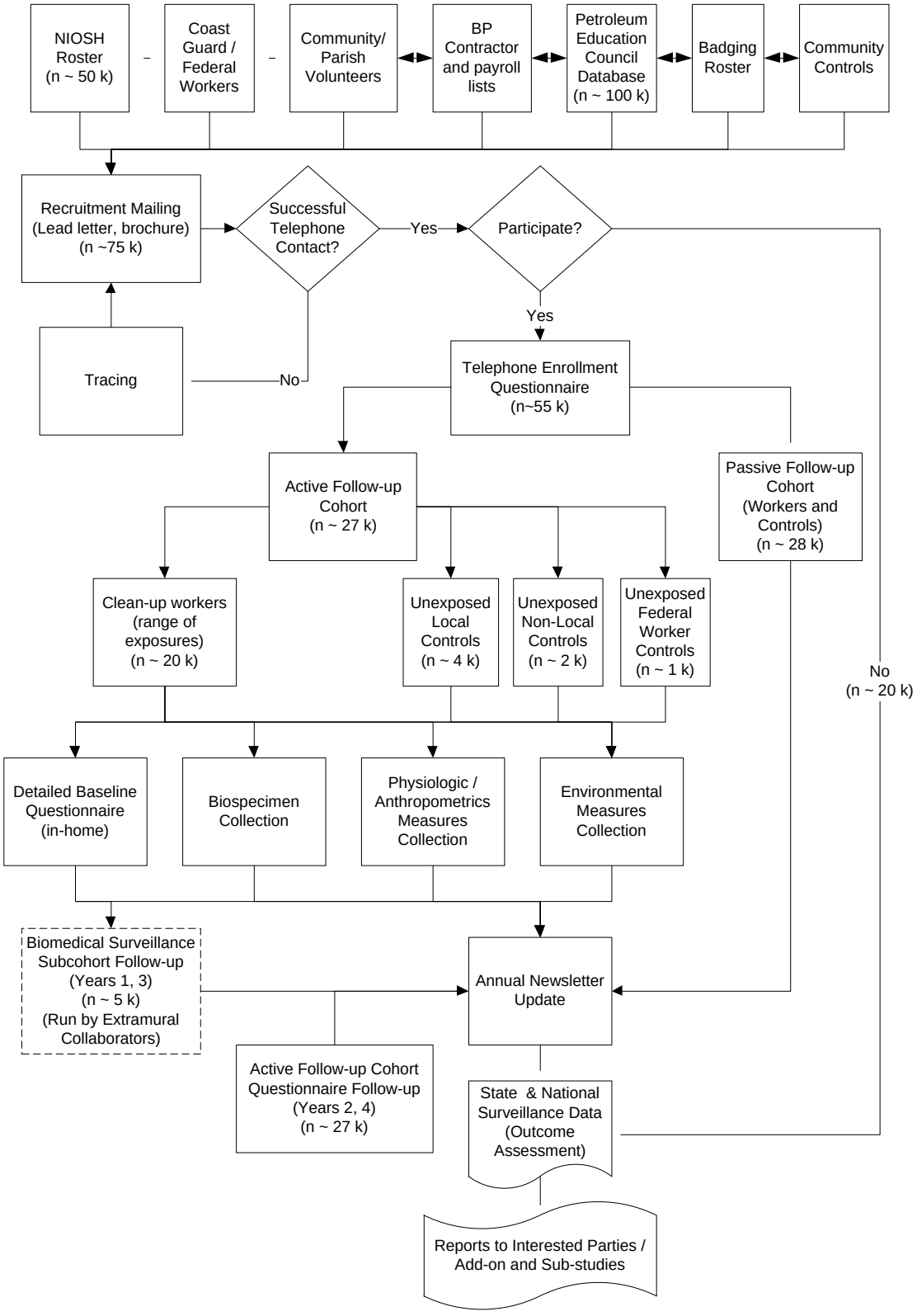
The Gulf Worker Study (GuLF) will investigate potential short- and long-term health effects associated with the clean-up activities of the oil spill among a cohort of workers and volunteers involved in the Deepwater Horizon disaster. Over 55,000 persons have participated to date in clean-up activities related to the spill. Crude oil, burning oil, and the dispersants used during clean-up efforts contain a range of known and suspected toxins. Exposures to persons involved in clean-up range from negligible to potentially significant, especially for workers involved in tasks associated with direct exposure to crude or burning oil, or to chemical dispersants. However, prediction of adverse health effects is not possible because the long-term human health consequences of oil spills are largely unknown due to the dearth of research in this area. The potential health effects associated with the levels of exposure experienced by clean-up workers are largely unstudied. Heat and stress experienced by these workers may also have adverse long-term health effects. In addition to the oil itself, the widespread economic and lifestyle disruption caused by the oil spill may contribute to mental health problems among this population.

The cohort will consist primarily of English, Spanish, or Vietnamese speaking adults who performed oil-spill clean-up-related work ("exposed") and similar persons who engaged in no clean-up-related work ("unexposed" controls). Accommodations for enrolling participants speaking other languages will be developed through community collaborations as appropriate. Workers will be sampled from across job/exposure groups. Participants will be recruited into either an *Active Follow-up Cohort* (N~27,000) or a *Passive Follow-up Cohort* (N~28,000). A *Biomedical Surveillance Sub-cohort* (N~5,000) will be nested within the Active Follow-up Cohort. Participants will be interviewed about their clean-up-related tasks, demographic and socioeconomic factors, occupational and health histories, psychosocial factors, and physical and mental health. Members of the Active Follow-up Cohort will also be asked to provide biological samples (blood, urine, hair, toe nail clippings, and possibly saliva) and environmental samples (house dust, tap water) and will have basic clinical measurements (height, weight, waist and hip circumference, blood pressure, FEV1/FVC) taken during home visits at enrollment. The Biomedical Surveillance Sub-cohort will participate in a more comprehensive clinical assessment after the initial home visit, including more comprehensive pulmonary function testing, neurological testing, and collection of additional biological and environmental samples. Exposures will be estimated using detailed job-exposure matrices developed from data from monitoring performed by different agencies and organizations during the crisis, information obtained by interview, and the available scientific literature. We will investigate acute health effects via self-report from the enrollment interview among all cohort members and via clinical measures and biological samples from Active Follow-up Cohort members. All cohort members will be followed for development of a range of health outcomes through record linkage (cancer, mortality) and possibly through linkage with routinely collected health surveillance data (collected by health departments and the CDC) or linkage to electronic medical records that may become available during the course of follow-up. Health outcomes among the Active Follow-up Cohort will also be identified through self-report via periodic follow-up interviews. Additional outcome information will be obtained on the Biomedical Surveillance Sub-cohort from periodic follow-up clinical evaluations (e.g., spirometry, neurological testing) and analysis of follow-up biospecimens (e.g., immunologic parameters, liver function, renal function, DNA damage). Clinical protocols for the Biomedical Surveillance Sub-cohort will be developed and carried out in

collaboration with local university partners identified through a request for proposals (RFP). Follow-up of the entire cohort is initially planned for 10 years, with extended follow-up possible depending upon scientific and public health needs and the availability of funds.

Recruitment of subjects should begin in late October 2010, with the telephone interviews expected to be completed within 9-12 months and the baseline home visits within 18 months. We will initially target workers residing in the five most affected Gulf States (LA, MS, AL, FL, and TX), although we may expand to other states if further information about the geographic distribution of workers and their exposures warrants additional follow-up in these states. We will work closely with a Community Advisory Board to develop community support for this study and appropriate communications and study materials.

Schematic of Study Design



1 Background Information and Scientific Rationale

There has been little research of the long-term health effects from oil spills. This is despite the fact that between 1970 and 2009, there were 356 spills of more than 700 tons from oil tankers, with approximately 38 of these spills affecting coastal populations [International Tanker Owners Pollution Federation Limited (ITOPF) 2009, Aguilera, et al. 2010]. The Deepwater Horizon disaster, with its release of approximately 5 million barrels (~680,000 tons) of crude oil into the Gulf of Mexico, is far larger than any of these tanker spills. Given the magnitude of this spill and the scope of the potential exposures – at least 55,000 workers involved in clean-up efforts and countless residents of the affected areas – study of the human health effects of this spill is urgently needed to monitor gulf clean-up workers and to understand the adverse consequences of oil spills in general.

Crude oil is a complex mixture containing a range of known and suspected toxins, including volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), hydrogen sulfide, and heavy metals. VOCs, particularly benzene, have been linked to lymphohematopoietic malignancies [Savitz and Andrews 1997, Hayes, et al. 2001, Glass, et al. 2003, Steinmaus, et al. 2008] and kidney dysfunction [Chang, et al. 2010]. They can also cause central nervous system depression, respiratory irritation, and immune system alterations [Kirkeleit, et al. 2006, Gillis, et al. 2007, Lee, et al. 2007, Cho 2008]. Naphthalene, which causes olfactory neuroblastomas, nasal tumors, and lung tumors in rodents, is listed as possibly carcinogenic to humans (Group 2B) by IARC [IARC 2002]. Polycyclic aromatic hydrocarbons (PAHs) include known carcinogens and may alter reproductive and immune functions [Agency for Toxic Substances and Disease Registry (ATSDR) 1995]. Hydrogen sulfide can cause acute and chronic CNS effects such as headaches, poor attention span, poor memory, and poor motor function [Agency for Toxic Substances and Disease Registry (ATSDR) 2006]. Heavy metals found in crude oil, including arsenic, cadmium, chromium, manganese, copper, nickel, vanadium, and lead, have a range of adverse health effects, including neurotoxicity and carcinogenicity, renal and immunotoxicity [ATSDR 1999, 2004, 2005, 2007a, 2007b, 2008a, 2008b, 2009, Hazen, et al. 2010, Camilli, et al. 2010, Botello, et al. 1997].

Burning oil produces particulates, which have adverse cardiac and respiratory effects, and may generate dioxins because of incomplete combustion in the presence of chlorine in the sea water (Howard 2010).

The dispersants used to break up the oil contain a number of respiratory irritants, including 2-butoxyethanol, propylene glycol, and sulfonic acid salts. Heat and stress experienced by the clean-up workers may also have adverse health effects. In addition to exposures from the oil itself, the widespread economic disruption caused by the oil spill may also contribute to mental health problems in a population with potentially increased vulnerability due to prior exposures to trauma, financial strain and social stressors arising from other recent disasters [Galea, et al. 2008]. Such stressors may also adversely impact physical health.

The few studies that have evaluated the human health consequences of oil spills have primarily focused on acute physical effects and psychological sequelae. These studies have examined the *Exxon Valdez* (Alaska, 1989), *Braer* (Shetland Islands, UK, 1993), *Sea Empress* (Wales, UK, 1996), *Nakhodka* (Oki Islands, Japan, 1997), *Erika* (Brittany, France, 1999), *Prestige* (Galicia, Spain, 2002) and *Tasman Spirit* (Karachi, Pakistan, 2003) oil tanker spills. Most of these studies were cross-sectional. A number of the

studies reported respiratory symptoms, including cough and shortness of breath [Carrasco, et al. 2006, Janjua, et al. 2006, Meo, et al. 2009, Sim, et al. 2010]. In a follow-up study among clean-up workers of the *Prestige* oil spill, Zock et al [2007] observed that lower respiratory tract symptoms persisted 1 to 2 years after exposure had ended (although the excess risk decreased with increasing time from last exposure) and that the symptoms showed exposure-response patterns in relation to number of exposed days, exposed hours per day, and number of activities. Meo et al [2008, 2009] reported a reduction in forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and forced expiratory flow and maximum voluntary ventilation (MVV), including exposure-response trends, in a small study of workers involved in the clean-up of the *Tasman Spirit* oil spill. Other commonly reported symptoms in these studies include itchy eyes, nausea/vomiting, dizziness, and headaches [Campbell, et al. 1993, Lyons, et al. 1999, Morita, et al. 1999, Carrasco, et al. 2006, Janjua, et al. 2006, Meo, et al. 2009, Sim, et al. 2010], and skin irritation/dermatitis [Campbell, et al. 1993, Janjua, et al. 2006, Sim, et al. 2010]. It is worth noting that, among Prestige oil spill clean-up workers, proper safety training was associated with greater use of protective equipment and a lower frequency of health problems [Carrasco, et al. 2006], which indicates that training can be effective in prevention.

In addition to health effects induced by chemical and physical exposures, physical and mental health may be adversely affected through pathways involving physiological and psychological responses to acute and chronic stressors related to the disaster. Adverse psychological consequences have frequently been linked to previous oil spills. Excess prevalence of generalized anxiety disorder, posttraumatic stress disorder (PTSD), and depressive symptoms were observed among communities affected by the *Exxon Valdez* oil spill approximately one year after the spill occurred [Palinkas, et al. 1993]. Similar patterns of higher anxiety and depression scores and worse mental health were observed among communities near the *Sea Empress* spill [Lyons, et al. 1999]. The *Braer* spill was associated with increased somatic symptoms, anxiety, and insomnia, but not personal dysfunction or severe depression [Campbell, et al. 1994]. Worse mental health scores were related to proximity to the *Prestige* spill [Sabucedo, et al. 2010].

In studying stress-related effects, it will be important to consider measures of mental health and biological response to evaluate both subjective and objective outcomes. In a community-based study of residents living near a petrochemical complex, perceived health was related to perceived risks due to chemical exposures, while inflammatory cytokine levels were related to objective proximity to the complex [Peek, et al. 2009]. In the same community, interviews after a petrochemical accident revealed significant decreases in perceived physical and mental health associated with multiple covariates, including lower education, distance and impact of the disaster [Peek, et al. 2008]. Susceptibility to the adverse effects of disasters may be increased by a variety of factors, including extent of exposure, female gender, middle age, ethnicity or minority status, pre-existing mental and physical health, economic and psychosocial resources [Norris, et al. 2002]. Consequently, the stress-related effects of the Deepwater Horizon Disaster may be amplified in a population still recovering from the impact of other recent disasters and in vulnerable subpopulations [King and Steinmann 2007, Galea, et al. 2008]. Research in the affected region also needs to take into account the unique history and potential vulnerability of migrants, ethnic or cultural minorities in the study population, e.g., Vietnamese [Palinkas, et al. 1992, Do, et al. 2009, Norris, et al. 2009].

Studies of genotoxicity and endocrine toxicity also point to potential adverse effects among oil spill clean-up workers. All but one of these studies were conducted among clean-up workers involved in the *Prestige* incident. Findings include significantly higher DNA damage, as measured by the comet assay, but not cytogenetic damage, as measured by the micronucleus test, among exposed individuals compared to controls, which was related to duration of exposure [Laffon, et al. 2006, Perez-Cadahia, et al. 2006]. Clean-up workers were also found to have significantly elevated blood levels of aluminum, nickel, and lead, but decreased levels of zinc [Perez-Cadahia, et al. 2008]. In addition, exposed workers had significant decreases in blood prolactin and cortisol levels [Perez-Cadahia, et al. 2007]. A recently published study of the Prestige cohort [Rodriguez-Trigo, et al. 2010] found an increased risk of structural chromosomal alterations in circulating lymphocytes among exposed workers two years after the spill. These results are consistent with studies showing increased DNA damage in relation to low level exposure to benzene [Bagryantseva, et al., Maffei, et al. 2005, Chen, et al. 2008, Fracasso, et al. 2010] and PAHs [Bagryantseva, et al., Novotna, et al. 2007, Gamboa, et al. 2008]. On the other hand, a study of persons affected by the *Braer* spill [Cole, et al. 1997] found no evidence of genotoxicity through either DNA adducts in peripheral blood mononuclear cells or mutations at the *HPRT* locus in T lymphocytes.

Studies of upstream petrochemical workers, who are likely to have many exposures similar to that of oil spill clean-up workers, have reported excesses of leukemia, multiple myeloma, and melanoma, and esophageal adenocarcinoma [Schnatter, et al. 1992, Kirkeleit, et al. 2008]. While such rare outcomes may be take years to develop, immediate and lasting changes may be seen in intermediate biomarkers indicating toxic effects and potential for future disease risk. The immune system may represent a particularly sensitive and accessible system for determining physiological impact of oil spill exposures. For example, the hematotoxic and immunotoxic effects of benzene exposure have been well described, occurring even at relatively low levels of exposure [Lan, et al. 2004]. These effects, indicated by downward shifts in leukocyte and red blood cell counts, may also be more apparent in susceptible subgroups defined by genetic variation in inflammatory, apoptotic, or metabolizing pathways [Lan, et al. 2005, Kim, et al. 2007, Lan, et al. 2009, Zhang, et al.]. Benzene's toxicity to hematopoietic progenitor cells may also impart long-term effects on the immune system leading to premature immunosenescence. This idea is supported by the finding that higher personal benzene exposures in traffic officers were associated with significantly shorter leukocyte DNA telomere length [Hoxha, et al. 2009], a marker of immune aging that has been related to risk of multiple chronic disease outcomes and mortality. Other intermediate markers related to chronic disease risk include inflammatory cytokines, antibodies indicating reduced immunity to latent viral infections, or auto-antibodies, though limited information exists on these measures in past studies of oil spill or petrochemical workers.

2 Study Objectives

This research effort is designed to investigate potential short- and long-term health effects among workers engaged in clean-up activities surrounding the Deepwater Horizon oil spill. Given the very limited health effects research conducted to date on oil spill clean-up workers, the GuLF Worker Study is designed not only to study a few narrow *a priori* hypotheses, but rather to allow the investigation of a wide range of potential adverse health effects, including physical, psychological, and biological effects. The long-term goal of this study is not only to identify adverse health outcomes related to

clean-up activities among the Deepwater Horizon responders, but also to assemble information that can be used for prevention and intervention of adverse health outcomes in any future similar disasters..

2.1 Primary Objective

The primary objective of the GuLF Worker Study is to assess a wide range of potential short- and long-term human health effects associated with clean-up and disposal activities surrounding the Deepwater Horizon oil spill in the Gulf of Mexico. Health areas of interest include, but are not limited to, respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, substance abuse, immunologic, hepatic, and renal effects. A key aspect of assessing these health effects will be to investigate biomarkers of potentially adverse biological effect, including DNA damage, aberrant epigenetic profiles, and alterations in gene expression, some of which have been observed in previous studies of oil spill clean-up workers.

2.2 Secondary Objectives

The secondary objectives of the study are to: 1) create a resource for additional collaborative research on specific scientific hypotheses or on subgroups of interest. We will work with external scientists to facilitate nested sub-studies within the existing cohort to examine outcomes and exposure subgroups of interest; and 2) create a resource to better understand the short and long-term human health effects of oil and oil dispersants in the environment.

2.3 Sub-study Objectives

At this time, one sub-study, the Biomedical Surveillance Sub-cohort, is planned as an integral part of the study proposal although the specific tests to be carried out and the implementation details are not yet designed. The detailed protocol (s) for this Sub-cohort will be developed in collaboration with extramural partners and will be separately peer-reviewed. Objectives of the Biomedical Surveillance Sub-cohort will include investigating immediate and ongoing physiological and clinical parameters in a group of highly exposed workers and a smaller number of unexposed workers. Establishing this exposure-enriched group with more detailed information on adverse outcomes and repeated biological measures will provide an important resource for longitudinal studies and enable nested comparisons with measures obtained on the larger cohort.

3 Study Design

3.1 Description of the Study Design

The GuLF Worker Study has been designed to allow investigation of potential short- and long-term health effects associated with the oil spill clean-up work and to create a resource for collaborative research on specific scientific hypotheses or subgroups. It is an observational prospective cohort study that will create opportunities for both analyses of the full cohort as well as numerous nested analyses. The design will enable

investigators to efficiently address specific hypotheses previously raised from oil spill exposures and, importantly for an exposure that has not been studied in relation to long-term health outcomes, allowing them more generally to identify new symptoms and conditions that may occur in excess among the exposed participants and determine the extent to which any physical and mental health conditions persist. The data and the biological and environmental samples that will be collected will allow examination of a wide range of health areas of interest, including respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, hepatic, and renal. The study is planned to be at least 10 years in duration, although it is anticipated that the study may continue for 20 years or more, through record linkage, at a minimum. Prospective studies typically have a long-term design because some diseases of interest, such as cancer, generally have long latency periods, e.g., 20 years or more. Consequently, we will consider extending this study at a later date, based on what we learn during the initial study period, scientific and public health needs, and on the availability of funds.

3.1.1 Study Population

To capture a representative sample of the clean-up workers and controls, we will target individuals across the various job/exposure categories from the Petroleum Education Council (PEC), NIOSH, or other worker/volunteer rosters and administrative lists. These individuals are potential participants because they are believed to have engaged in clean-up work or participated in worker training modules in anticipation of such work. We will exclude individuals such as journalists who did not engage in clean-up activities but were required to undergo safety training to gain access to worker staging areas (and, therefore, may appear on the PEC list). These individuals will be determined from either the training lists (i.e., individuals who indicated that they intended to work for less than one week) or via screening questions during the enrollment telephone interview. We define *exposed* subjects as individuals who completed at least one day of oil-spill clean-up-related work, either paid or volunteer. We define *unexposed* subjects as eligible individuals who completed safety training in anticipation of performing clean-up work but did not do so. Selection for active follow-up will cover all levels of potential exposure but will preferentially select workers with the greatest likelihood of exposure to oil and oil byproducts. We will conduct interviews in English, Spanish, and Vietnamese. Special accommodation will be made for those speaking other languages, if feasible and warranted by the numbers. PEC training was conducted in English, Spanish, and Vietnamese only.

3.1.2 Study Cohorts

After administering a screening enrollment questionnaire to all potential cohort members, we will recruit individuals into either a *Passive Follow-up Cohort* (N~29,000) or an *Active Follow-up Cohort* (N~27,000). A *Biomedical Surveillance Sub-cohort* (N~5,000) will be nested within the Active Follow-up Cohort. The design with active and passive sub-cohorts will allow an efficient and cost effect way to include most of the clean-up workers into a prospective study and also to obtain comprehensive and detailed clinical and biologic information on a scientifically adequate sample of the total group. The study effort, participant commitment, and potential knowledge gain increases from the Passive Follow-up Cohort to the Active Follow-up Cohort to the Biomedical Surveillance Sub-cohort. For each cohort/sub-cohort, we will oversample from job categories that likely

resulted in higher exposures and/or were smaller to ensure adequate representation of all tasks performed.

Workers will primarily be identified through the NIOSH safety training roster, but supplemented with additional workers identified through the PEC list and other lists that may become available of persons who may have been involved in clean-up activities (see Section 3.3.1 for a description of the lists of potential subjects.)

The *Active Follow-up Cohort* will contain ~20,000 workers (exposed) from across all job categories and ~7,000 controls (unexposed). This cohort may be largely restricted to persons residing in one of the five Gulf States primarily engaged in clean-up activities (LA, MS, AL, FL and TX), prioritizing workers closest to the spill area. Based on preliminary data on approximately 15,000 workers from the NIOSH roster, all but 5% of workers were from these five states. Eligibility may later be expanded to include other states based on information on the geographic distribution of workers that we will receive in the full NIOSH worker roster or from other worker lists. We will recruit workers from other states only if it is determined, upon receipt of the potential subject lists that a large number of highly exposed workers came from a given state. For logistical reasons, we will not recruit non-Federal employee controls from outside of the Gulf States. Federal workers (e.g. Coast Guard, OSHA, Fish and Wildlife, NOAA, EPA and others) residing outside of the five Gulf States will be included. A Federal control group of ~1,000 workers will also be recruited from among individuals eligible for clean-up work but ultimately not deployed. We will oversample certain job/exposure categories of particular interest (e.g., those with direct exposure to fresh crude or burning oil or to chemical dispersants). Target numbers for these job/exposure categories will depend on the distribution of jobs/exposures, which will be determined through the telephone interviewing, and on statistical power. Participants in the Active Follow-up Cohort will 1) be administered detailed interviews, 2) provide biological samples (blood, urine, hair, toe nail clippings, and possibly saliva) and environmental samples (house dust and tap water), and 3) have basic clinical measurements taken at enrollment, and 4) will be administered two follow-up interviews. In contrast, members of the Passive Follow-up Cohort will be administered only a brief telephone interview at enrollment. Disease and mortality during follow-up will be obtained via linkage with cancer registries and State vital statistics records.

The controls will preferentially be drawn from the PEC/NIOSH lists, which include some individuals who were trained but did not engage in clean-up work but were otherwise eligible. At some time during the peak work weeks, employers were advised that heat related health issues might be especially problematic for obese workers or those with high blood pressure. Although pre-employment screening may have been advised, it is uncertain whether or not it was systematically carried out, and if done, may have been contractor specific. Therefore, because some potential workers may have been turned away due to health concerns, potential controls will be asked why they did not participate in clean-up activities. Those indicating they did not qualify for medical reasons will be excluded as will those who completed training to facilitate receipt of a badge, with no intention of performing any clean-up related tasks. Should these lists yield insufficient numbers of unexposed individuals, we will explore strategies to identify unexposed community residents through friends/relatives identified by workers in the cohort or though neighborhood or telephone sampling (e.g. random digit dialing).

Because some workers from the five Gulf states will come from areas away from the affected communities and because controls from the affected communities may have experienced some spill-related exposures, including stress and social disruption, we will

establish two control groups. Persons from the lists described in Section 3.3.1 who are determined to have not engaged in clean-up activities and are eligible for this study will be placed in either a "local" control group or a "non-local" control group. The "local" control group will consist of controls residing within the affected communities. Their inclusions in analyses of the health effects of chemical exposures will account for the stress and other psychosocial factors experienced by clean-up workers residing in the affected communities. The "non-local" control group will consist of individuals residing within the affected states, but outside of the affected communities. These individuals will serve as a control group in evaluation of spill-related stress and other societal effects that may affect both exposed clean-up workers and unexposed controls residing in the affected communities. Based on residence information from the first 15,000 persons in the NIOSH Roster, it appears that the majority of trainees on the PEC/NIOSH list who are eligible to serve as controls will be disproportionately from the affected communities; consequently, we will oversample "non-local" trainee controls to provide sufficient statistical power for analyses involving this group. A third smaller control group will be established from among Federal workers (e.g. Coast Guard) who were eligible to participate in clean-up but were not deployed. Federal workers involved in the clean-up effort represent a number of agencies and may come from states outside of the Gulf. For logistical reasons, we will recruit shared controls for all Federal workers (i.e., from a subset of Federal agencies involved in the clean-up). We will work with the agency representatives to identify a source of controls that best represents these various workers, such as Coast Guard members or Fish and Wildlife Service workers who were not sent to the Gulf for clean-up operations but were otherwise eligible or given notice of potential deployment.

The *Passive Follow-up Cohort* will contain individuals who completed an enrollment interview but were not included in the Active Follow-up Cohort because 1) they did not reside in one of the targeted Gulf States, 2) the target number of individuals from their job/exposure category was already enrolled, or 3), they are unable or unwilling to participate in active follow-up but are willing to be tracked over time. Outcomes follow-up will be obtained via linkage with State cancer registries and vital statistics databases.

The *Biomedical Surveillance Sub-cohort* will be an intensively evaluated subgroup nested within the Active Follow-up Cohort. It will be sampled from across the job/exposure groups and from controls, but with oversampling of the most highly exposed workers. Potential members of this sub-cohort will be identified during the enrollment interview, based on their reported clean-up activities. To achieve our target of ~5,000 members in this sub-cohort, we will identify ~6,250 potential members during the enrollment interview, assuming that ~80% will ultimately agree to participate in the further procedures required of the Biomedical Surveillance Sub-cohort when they are recontacted later by extramural collaborators. This sub-cohort will undergo the same baseline and follow-up procedures as the rest of the Active Follow-up Cohort, but will additionally participate in multiple follow-up visits involving health assessments that include spirometry with bronchodilator challenge and neurological testing and collection of repeat biological and environmental samples. This sub-cohort will undergo more intensive biomonitoring than the rest of the Active Follow-up Cohort, including having their CBCs and WBC differentials measured at baseline. Clinical protocols for the additional clinical examinations will be developed and implemented in collaboration with local university partners identified through a request for proposals (RFP) and, therefore, will not be discussed further in this protocol. These will undergo separate scientific and IRB review. Consideration will be given to focusing on the more highly exposed Gulf States (e.g. Louisiana and Alabama) to facilitate comprehensive health examinations.

We anticipate a standardized core protocol with room for unique investigator initiated options to address additional hypotheses.

3.1.3 Exposure Reconstruction

Although monitoring data will be available on some individuals for some exposures, most participants in the study cohorts will lack such measurements. Because it is critical to have some indication of quantitative levels of exposure, it will be necessary to construct exposure indicators from the available monitoring data, characteristics of clean-up tasks, and work locations. A panel of industrial hygienists will be assembled to construct job-exposure matrices for the exposures of interest using monitoring data from multiple sources. These monitoring data, including individual measurements for some workers, area measurements, and Health Hazard Evaluations, were collected during clean-up activities by OSHA, NIOSH, NOAA, EPA, Fish and Wildlife Service, US Geologic Survey, the Coast Guard, and BP. In addition, available chemical analysis data of oil from the well and weather data from the period of the spill clean-up will be considered in relation to exposure opportunities. This information will be assembled for the exposure panel and used in exposure estimation and reconstruction. Exposures will be estimated for all included workers, including those from Federal agencies/institutions. We will also use environmental samples (house dust, tap water) and questionnaire data to identify relevant occupational and non-occupational exposures. Lastly, we will evaluate existing exposure measures on beach clean-up workers and consider collection of additional biomonitoring data for this large subgroup if clean-up efforts are still underway at the time of cohort enrollment. A detailed protocol of exposure assessment procedures will be developed by the study investigators in collaboration with the panel of industrial hygienists.

3.2 Eligibility Criteria

We anticipate screening as many as 80,000 individuals in order to recruit approximately 55,000 volunteers primarily from five Gulf States* (LA, MS, AL, FL and TX) into an active and passive follow-up cohort. Eligibility criteria for both the active and passive follow-up cohorts include:

- 18 years of age or older
- Speak English, Spanish, or Vietnamese
- Not medically excluded from participating in clean-up activities
- Fall into one of two oil-related exposure categories:
    - *Exposed* subjects must have completed at least one day of oil-spill clean-up-related work (other than safety training), either paid or volunteer.
    - *Unexposed* subjects will be individuals who completed safety training in anticipation of performing clean-up work but did not perform any clean-up related tasks, or other unexposed individuals invited to participate, if needed.

Determination of individuals who will be in the active or passive cohort will be made based primarily on level of exposure. Those who respond that they are engaged in oil

clean-up related activities that are suspected of having high exposures will automatically be invited to enroll in the active follow-up cohort (e.g. working at the source, skimming, incineration, booming, wildlife clean-up, etc.). Those engaged in activities suspected of being associated with lower exposure will be scrutinized to determine whether to enroll them into the active or passive follow-up cohort. The number of other individuals already enrolled in the active cohort by state and work task will also be considered in additional inclusions into the active cohort.

*Note: If there are a substantial number of individuals who live out of state and are suspected to have significant exposures, we will extend our efforts to enroll these suspected high-exposed individuals into the active follow-up cohort. However, at this time, the numbers of individuals living outside of the Gulf States and engaged in clean-up related activities appears so low (< 5% from all remaining states combined) that it is not logistically feasible to enroll them into the active follow-up cohort. Instead, these individuals will be enrolled into the passive follow-up cohort.

3.2.1 Rationale for including only workers or those who were trained

Morbidity and mortality rates from the general population include individuals who are often too sick to work. Thus, those who are hired, or trained to be hired, are generally healthier than those who aren't trained because relatively healthy individuals are more likely to gain employment and remain employed – a phenomenon known as the "healthy worker effect." The healthy worker effect is particularly relevant in the selection of unexposed controls. In order to obtain comparable controls for workers engaged in oil spill clean-up activities, we would need to find individuals who otherwise would have been able to work (i.e., were healthy enough to work), but weren't hired to do so, thus limiting their exposure. We plan to recruit from a master list that incorporates training and badging information (e.g., the NIOSH roster, PEC training lists, Coast Guard deployment logs, etc.) to identify workers who were trained and medically cleared to participate but may or may not have been engaged in clean-up activities ("exposed" and "unexposed," respectively). Since everyone in the spill area was required to have a badge, and completion of a basic training module was required to receive a badge, volunteers should have also completed one or more training modules before engaging in clean-up activities. Others who worked but were not trained through the PEC will also be eligible. This includes workers whose training was separately administered through Parish organizations and individuals who might not have completed required training modules for language or other reasons (e.g. crew on Vessels of Opportunity whose captains, only, received formal worker training).

While exposed and non-exposed individuals will be recruited during the same enrollment period, if we aren't able to find suitable non-exposed individuals from this master list, we will seek matched controls in the community through references provided by the participants themselves, individuals from the BP claims databases, or other community selection techniques such as random digit dialing. This may involve more time than identification of controls from the clean-up training lists. We have planned for these activities to occur in the later months of recruitment so that we can focus on enrolling exposed workers first.

We will actively enroll any individual, 18 years or older, who is on a worker or volunteer list describing any potential contact with oil and dispersants, regardless of their gender, racial and ethnic background, or pregnancy status. Approximately 17% of the first 15,000 workers enumerated by NIOSH were women. Although we do not anticipate a

large pregnant population, there may be individuals who were not aware that they were pregnant or who otherwise engaged in clean-up related activities despite knowing that they were pregnant and who may be recruited into the study. Others may have subsequently become pregnant. In order to obtain data that won't be confounded by the effects of pregnancy, pregnant women will not undergo active follow-up study procedures until they are at least three months post-partum.

3.2.2 Rationale for Exclusions

Participant selection and rationale for eligibility criteria have been described in detail in Section 3.2 - Eligibility Criteria. Enrollment is open to adults of all racial and ethnic background. Children will not be enrolled because they were not allowed to participate in clean-up activities. Study activities present minimal risk to pregnant women. Therefore, pregnant women will be allowed to enroll in the study, and women who become pregnant during the study will not be withdrawn.

Those who were deemed medically ineligible to participate in clean-up activities because of pre-existing conditions are excluded because they won't be representative of those individuals who were engaged in clean-up activities.

3.3 Recruitment

3.3.1 Recruitment Database

The cohort will be recruited over a 9-12 -month period, starting in late October 2010 with the baseline home visits completed within 18 months and will initially be followed annually for at least 10 years. (We anticipate that the cohort will be followed for up to 20 years to extract the maximum information from a study with a prospective design). Potential participants will be identified from the existing NIOSH Voluntary Worker Roster (N~55,000) which is being shared with NIEHS through a Data Transfer Agreement. The NIOSH Roster is believed to contain a large majority of the workers who engaged in clean-up activities. We will seek access to the larger PEC list of individuals who completed one or more safety training modules (N~100,000) as well as other known lists of individuals involved in clean-up activities (e.g., parish responder lists, BP contractor payroll, and lists of Federal workers and contractors deployed to, or otherwise engaged in, on-site clean-up activities in, the Gulf, including the Coast Guard, OSHA, NIOSH, NOAA, EPA, Fish and Wildlife Service, US Geologic Survey, National Guard, etc.). Because the NIOSH Roster was developed in connection with worker training, it is expected that most, if not all, names from the Roster will be included on the PEC list. Many, but not necessarily all, of those identified through Federal worker lists will also appear on the PEC list. Some workers trained through Parish organizations and crew members on Vessels of Opportunity are not expected to be found on the PEC list. The PEC list may include some duplicate names as a few workers were required to complete additional training modules at a later date as workplace hazards were identified. Some of these lists, such as those of employees of Federal agencies/institutions, will contain mostly, if not entirely, persons involved in clean-up operations; other lists, such as the PEC list, will include a substantial proportion of persons who did not participate in clean-up (but may have taken the safety training in anticipation of doing so) and can be identified only at the time of the telephone interview. Because members of some Federal agencies participated in agency-specific safety training and, therefore, may not appear

on the NIOSH or PEC safety training lists, from which we will draw our controls, we will work with the Federal agencies to identify employees who did not participate in clean-up operations but would have been eligible to do so and invite them to participate in this study as controls. We will work as quickly and efficiently as possible with collaborating partners and other federal agencies in obtaining access to these lists. Time is of the essence because we wish to interview clean-up workers and collect biologic and environmental samples during clean-up activities or as shortly thereafter as possible. This is necessary because biologic indicators of exposure dissipate with time and individual's recall of their activities also diminishes.

These databases will be merged into a master recruitment file to identify and remove duplicates. We expect a total of about 110,000 names from the PEC list and other worker lists which we are assuming will be reduced to about 80,000 after eliminating duplicate names and, if possible, those who completed training only to obtain access to the spill site, with no intention of engaging in clean-up work (e.g. reporters, government visitors, etc.). Where possible, we will infer potential exposure through the training the individuals obtained, their reported or anticipated activities (collected on the NIOSH Roster), and/or location in which they reported for work. However, we may not be able to definitively confirm oil spill clean-up related activities until we interview the participant and ascertain the types of activities that they performed. Thus, initial exposure characterization will involve a two-stage process where a participant is flagged for potentially being exposed/non-exposed which may later be modified based on information from the telephone enrollment questionnaire will include a series of questions which will ascertain exposure. Exposure classification for enrollment purposes into the active- or passive- follow-up cohort will be based on the participant's answers to these exposure questions. We will try to identify and prioritize enrollment of individuals with likely exposures so that we can better characterize their exposures, but given the limitation of not knowing a participant's true exposure status prior to their interview, we will most likely be enrolling exposed participants and unexposed controls at a comparable rate.

3.4 Community and Scientific Outreach

The goal of the community outreach efforts is to fully apprise the community of study activities, to ensure community collaboration and support in all aspects of the study including design, implementation, evaluation, translation, and to dissemination findings and results. Close and ongoing community engagement is expected to enhance the scientific validity of the study, make it more broadly relevant from a public health perspective, and expand its benefits to the affected communities.

3.4.1 Meetings with potentially affected groups

Before finalizing the study design, we will meet with community organizations, advocacy groups, and state and local government representatives to identify the primary health issues of concerns locally and discuss study implementation issues. Several of these community stakeholder groups have been identified across the five state area and we have already established contacts with many of these organizations and are continuing to solicit contacts with additional groups.

We have plans for a series of meeting with state and local health department representatives as well as the NGOs that span the various occupational groups

representing the workers involved in clean-up throughout the Gulf. We have meetings planned in Mississippi and Alabama during the week of September 12; Florida on September 23 and Louisiana the week of October 3. We are currently working to schedule meetings in Texas.

The groups span cultural, religious, occupational and state and local government sectors and are continuously updated as more information and contacts are made (current as of 9/7/2010). The groups listed below are examples of some of the groups that we have identified and established contact with:

- Alliance Institute
- Asian Americans for Change, Mississippi
- Bayou Grace Community Services
- Bayou Interfaith Shared Community Organizing (BISCO)
- Boat People SOS (BPSOS)
- Commercial Fisherman of America
- Gulf Coast Fund for Community Renewal and Ecological Health (GCF)
- Gulf Restoration Network
- Isle de Jean Charles Band of the Biloxi Chitimacha
- Louisiana Bayoukeeper
- Louisiana Bucket Brigade
- Louisiana Disaster Recovery Foundation, Oil Spill Recovery Policy & Advocacy Initiative
- Louisiana Justice Institute
- Louisiana Oystermen Association
- Louisiana Shrimp Association
- Mary Queen of Vietnam Community Development Corporation (MQVN CDC)
- Mississippi Center for Justice
- Mississippi Commission on Volunteer Service
- Mobile BayKeeper
- Moving Forward Gulf Coast, Inc.
- Parish Presidents
- South Bay Communities Alliance, Inc.
- SeaGrant Programs in LA, MS and AL
- State and local government representatives
- St. Bernard Project
- Steps Coalition
- The Village/El Pueblo
- Tri-Coastal Community Outreach
- Turkey Creek Community Initiatives
- United Commercial Fisherman Association of Louisiana
- United Houma Nation
- Vietnamese American Young Leaders Association of New Orleans
- Vietnamese Martyr's Church

Webinars. NIEHS hosted a 90-minute webinar with local researchers, community organizations and others interested in the GuLF Worker Study on August 17, 2010. The purpose of the webinar was to announce for the first time publicly the plans for the GuLF Worker Study and obtain feedback on study design and implementation from interested stakeholders. Prior to the webinar, NIEHS distributed a draft GuLF Worker Study Concept document and a Key Points document. The webinar was well attended by over 100 participants and we have received multiple offers from community organizations to provide assistance for the study. Suggestions made during and after the webinar have been incorporated into the study design. Additional webinars are planned for September 15 and other future dates to be determined to continue information exchange and dialog.

Phone briefing. As a follow-up to the first webinar and next step in the community outreach efforts, we will invite key stakeholder groups identified, such as from the list above to a follow-up phone briefing. The purpose of the phone briefing is to meet individually with each stakeholder group to review the study aims and implementation, answer any question or concerns about the study, establish a dialog with stakeholders, and begin discussions on the primary health issues of concern for their constituents. Approximately 10-15 phone briefings will be conducted each lasting up to 30 minutes. At the end of the call, we will document any action items and discuss plans for future meetings in person.

In-person meetings. As a follow-on to the phone briefings, we will travel to the five Gulf States to meet in person with the community stakeholder groups. During the in-person sessions, we will request to meet both with organizational leadership in addition to their constituents. The purpose of these meetings is to further build strong community ties and gather information to finalize the study design. Due to the short timeline to study launch we will immediately conduct informal discussions with leadership and listening sessions with their constituents. The topics of these discussions are expected to broadly include possible barriers to study implementation, resolutions to those barriers and the best methods to communicate with study participants and publicize the study.

HRSA and State Health Department meetings. Meetings are planned with State and local Health Department representatives beginning the second week in September, including a combined meeting of leadership from Health Service Regions covering the Gulf States on September 9-10. These meetings are intended to inform state and local leadership about study plans and to obtain input into study design and implementation. A specific focus of these meetings will be developing strategies for community based health and mental health referrals for participants identified as needing follow-up medical care (e.g. for follow-up of elevated blood pressure, or glucosuria) or identified as having unmet mental health or social service needs. While the GuLF Worker Study is not designed to provide medical care to its participants, we will work closely with local health officials to provide the appropriate referral information to participants identified as having unmet medical needs.

Dockside Chats. Study staff joined the Unified Command in several Dockside chats with workers during the week of August 22, 2010. These informal sessions provided insight into some of the health and community concerns of workers from the affected region.

3.4.2 Community Advisory Group

A Community Advisory Group will be created to provide advice on the study and outreach efforts. The group will consist of up to 15 members representing communities

from all five states as well as various occupational groups and is expected to engage in the following activities:

- Facilitate dialogue between community members and the study team
- Identify effective communication strategies and vehicles tailored to the communities' needs
- Assist in the dissemination of study related information locally and regionally
- Host community neighborhood meetings
- Proactively identify issues of concern with study implementation and options for resolutions
- Retention of participants in the study over time

The Community Advisory Group will meet regularly throughout the entire study duration. Meetings are expected to occur more frequently during study planning and initiation (i.e., monthly) and then less frequently in the out years of the study (i.e., twice annually).

3.4.3 Communicating the Study to the Community

Communication of the study activities to oil spill clean-up workers and affected communities is essential. Many of these efforts will involve communications through community leaders directly to their constituents, some will involve targeted outreach by the study and NIEHS and other efforts will involve media-based outreach. Typically, it takes multiple points of contact to motivate an individual to participate in a health study, particularly a longitudinal health study and to build study credibility. Although we will be working from a known population of oil spill clean-up workers, media-based efforts will afford the study legitimacy in an environment fraught with competing Katrina-focused studies, distrust of the government, and scientific complexity. Additionally, media-based outreach in conjunction with more direct-to-worker outreach will allow for the ability to reach a larger number of individuals in a very short time frame. The Community Advisory Group will be crucial in designing this process and enhancing its effectiveness.

Brochure. A study brochure has been developed in English, Spanish and Vietnamese. The purpose of the brochure is to introduce the study and provide contact information though the hotline and website. The brochure will be sent with the lead letter inviting study participants during enrollment but may also serve a variety of other purposes for community outreach.

Hotline. We will establish a toll free hotline for the study. During enrollment, the hotline will be used for workers to return a call to participate in the study. A call center representative will answer the hotline during call center hours of operation, i.e. from 9 AM to 9 PM, Monday through Saturday and from 12 noon to 6 PM on Sundays. It will roll to an answering machine after hours with all calls to potential participants returned the following day. Call center hours will be determined based on input from the community groups as to what would be acceptable.

Internet. We will maintain a website to provide information about the study. The website will be updated regularly with details on recruitment efforts, study findings, and links to other organizations and information resources. Additionally, we will seek to have each of our community partners have a link on their website to the study website. We will also

explore the possibility of using Web 2.0 resources such as Facebook and Twitter if we can be assured that participant confidentiality can be maintained and there are sufficient numbers of individuals within our study population and community who would be using these sites.

Advertising. Additional forms of media-based advertising will be determined in collaboration with key stakeholder groups. Radio may provide a good medium for communicating the study to certain segments of the population while billboard ads may appeal better to another. Whenever feasible, we will capitalize on opportunities to collaborate with community partners on radio or TV show interviews, local newspaper articles, and other media as a form of generating awareness and credibility for the study.

3.4.4 Scientific Outreach

The Webinars specifically targeted members of the scientific community, including researchers from local universities, NIEHS grantees, and researchers with past experience studying communities involved in other environmental disasters such as the World Trade Center cohort. The study concept was reviewed by the NIH IC Directors at a regularly scheduled meeting. An early draft of the protocol outline was reviewed at a meeting August 12 with NIOSH and CDC. The proposal was discussed August 19 at a meeting of multiple federal agencies involved in some aspect of the Oil Spill response. Suggestions received during those meetings have been incorporated into the current protocol draft. The proposed study builds on ideas generated during a scientific meeting hosted by the Institute of Medicine on June 22. In addition to undergoing scientific peer-review prior to submission of the study for NIEH IRB review, the study will receive additional review by an Institute of Medicine panel at a meeting to be held September 22. Additionally presentations of the study design have been (and will continue to be) made to a number of Federal panels and committees (e.g. *ASTHO). The Institute of Medicine is expected to provide ongoing scientific oversight. Oversight will also be provided (see below) by a Scientific Advisory Board appointed by the Chair of the NIEHS Board of Scientific Counselors, operating as a subcommittee of that Board.*

3.5 Enrollment Procedures and Enrollment Questionnaire

Initial contact with participants will be through a one-page lead letter and brochure which will briefly outline the study purpose, study benefits, study sponsorship, contractor name, what will be asked of the participant, compensation if they participate, confidentiality assurance, importance of their participation and contacting information if they would like more information (contact names and web site address). Every attempt will be made to have the lead letter have the same message in English and either Spanish or Vietnamese, using both the front and back of the page. The lead letter will introduce the enclosed four-color, tri-fold study brochure which will contain instructional graphics and more details of the study. The lead letter and brochure will both point to the website address for additional information.

The telephone contact schedule will be coordinated with the lead letter mailing by parsing the sample into batches and working the mailing and then calling one a batch at a time. Mailing of letters to each batch of names will precede calling by several days to allow the letter and brochure to be delivered. The letter envelopes will request USPS to forward mail and to provide us with an address update. Mail returned as undeliverable and with address update notifications will be flagged for tracing.

Several days after the lead letter mailings, the associated telephone numbers will be released to telephone interviewers to commence screening and enrollment dialing and interviewing. Interviewers will discover unusable telephone numbers – fast busy, disconnected, no one by that name, etc. Telephone numbers with outcome codes indicating they are unusable will be flagged for tracing. The telephone number management system will apply calling algorithm rules to each telephone number based on the pattern of interim outcome codes assigned by the interviewers at each dialing (e.g., no more than two calls per day), varied times of day and weekend, weekend only, once-a-day only, wait for a cool down period (initial refusal), scheduled call-backs, soft appointments, etc. The telephone number management system will enforce these rules when delivering telephone numbers to the interviewers. Calls will be conducted from 9 AM to 9 PM (local), Monday through Saturday, and 12 PM to 6 PM (local) on Sunday, if acceptable to the community.

The interviewing staff will include a group of interviewers who are bilingual in English and either Spanish or Vietnamese. We will attempt to identify the primary language of each potential participant in advance of assigning calls to interviewers by considering surname and other information that may be available in the master recruitment dataset (e.g. variable indicating primary language in the NIOSH roster data). Potential participants will be assigned to an interviewer who is fluent in their primary language and English. In some cases, the call assignment process may fail to overcome language barriers between the interviewer and the participant, and the interviewer may be forced to abort the call. If the call is aborted, the interviewer will make notes about the call and attempt to classify the primary language of the potential participant so that the call can be reassigned to the appropriate interviewer.

The entire screening and enrollment telephone call will take approximately 30 minutes to complete. Should the respondent be selected for active follow-up and agree to participate, their contact information and scheduling information will be transmitted to one of 14 regionally distributed clinical field supervisors who will assign the respondent to the most geographically proximate Home Visit Agents (HVA) under their supervision.

3.6 Tracing

Tracing will be conducted if we are unable to contact the participant by telephone or reach them through the contact person they named on the NIOSH roster data. Participants who cannot be initially reached with roster information will be flagged and submitted for tracing in monthly batches. Fortunately, we have cell phone numbers (at least for those listed on the NIOSH Roster) which should significantly improve our ability to contact participants. However, we are aware that participants may follow regional practices found post Katrina and use “disposable” cell phones only for the time needed. We have projected the need to conduct locating as much as 15 percent of the sample and expect that we subsequently will be unsuccessful in tracing 5 percent of this group. Recruitment and tracing efforts will be carried about by different staff members so that the time required for tracing does not disrupt the recruitment process.

Rigorous locating operations will be instituted to reach study participants based on the contact information obtained through the automated batch tracing databases, such as Lexis Nexis Accurit, Telematch, Pension Benefit Information, National Change of Address, and Trans-union as well as InfoUSA and Experian.

3.7 Procedures for Enrolling Active and Passive Cohort

Participants included into the active cohort are those who self-identify being exposed to oil, oil byproducts, and chemical dispersants through their clean-up related activities during the enrollment interview. Additionally, controls will be enrolled into the active cohort until the subgroup quotas are filled.

The Passive Cohort members are those who complete the screening questionnaire in a quota group that is already filled, or who decline to participate in active follow-up. They will have given verbal consent for completing the telephone interview, providing annual updates on contact information, and having their health and vital status tracked via electronic data. The Passive Cohort will include individuals across the range of exposures, including those who are not exposed. Since this cohort will include persons not selected into the active cohort, the passive cohort is likely to be disproportionately weighted towards those less likely to have been exposed to oil-spill related chemicals.

3.7.1 Recruitment and Retention

Effective recruitment is critical to the success of this study yet the nature of the study population, protocol, and the long follow-up period present inherent challenges to recruiting and retention. A multi-faceted approach to participant recruitment and retention will take into account best practices in the participant recruitment literature as well as proven methods utilized in past studies conducted in similar populations.

Participation rates in health studies and surveys have been declining for the last several decades. This general trend serves as backdrop to several specific challenges inherent to this study.

One significant challenge in recruiting and retaining participants will be to address the unique circumstances faced by Gulf Coast families both prior and subsequent to the Deepwater Horizon Oil Spill. Many of the affected communities were already under economic stress because of hurricane Katrina and the recent recession, which makes it difficult to engage them in research even under the best circumstances. Gulf Coast families are experiencing further environmental, financial, and health-related impacts since the disaster. Recruitment and retention strategies must take into account these day-to-day circumstances and other obligations such as employment, childcare, etc. to mitigate known barriers to participation.

A related challenge will lie in gaining credibility and cooperation from a population that may be wary of research studies conducted by outsiders, particularly government-based studies. It will be important to demonstrate an understanding of the circumstances these individuals face. Recruitment strategies are needed that position the team to capitalize on community outreach efforts as well as efforts to brand the study as something other than “just another government study.” As with all studies, potential participants may be reluctant or unable to spend the time or experience the inconvenience involved in study participation. Recruitment strategies are needed to overcome these sources of reluctance and present the study as beneficial.

After participants are enrolled in the study, maintaining their continued participation over the full follow-up period is critical. Participants will relocate, experience family disruptions such as divorce, death or illness, undergo economic changes, and realize logistical

difficulties. Strategies are needed that motivate continued participation and alleviate logistical constraints.

For all of these reasons, this study will develop a comprehensive recruiting and retention plan designed to maximize participation for the entire duration of the study with assistance from the Scientific and Community Advisory Committees, while using study resources efficiently. Although monetary incentives are necessary, an array of other strategies will be applied to cultivate a sense of loyalty, commitment, and appreciation among study participants and oil-spill communities to the study..

3.7.2 Recruitment/Retention Strategies and Approach

Importance. Recruitment interviewers will be trained to convey an appropriate sense of the importance of the research among both exposed and unexposed individuals. This importance relates not only to the oil spill, but also, more generally, to all of the health, environmental, and psychosocial impacts (e.g., displacement, stress, exposures) associated with disasters, ultimately to support a better understanding of how to respond to such disasters. This will be reinforced throughout the study with communications from health officials and study investigators.

Direct Benefit. The main benefit is pride in having participated in an important public health research effort for their communities. Participants will receive some results from the medical testing. Recruitment approaches will be designed to minimize any potential gap in perceived study benefit between the exposed and unexposed.

Study Identification and Branding. The study will be presented publicly in a manner that appropriately conveys its importance both to participants and to other audiences.

The study website will include information for the public as well as a place for participants to learn more about the study, receive important study information, schedule visits, update contact information, and pose questions to a health professional. Scientific publications and results will be posted on the website.

News items and press releases will announce and publicize the study while reflecting local interest group and health department participation. Participants will also receive annual newsletters to keep them informed about the progress of the study.

3.8 Recruitment of Special Populations

Based on data from the first part of the NIOSH roster and from reports from the field, we are currently planning to recruit Vietnamese, Spanish, and English speaking participants. Speakers of other languages may be targeted later through RFPs (and funded via subcontracts), as described below. Depending on the numbers of individuals in specific exposure groups who do not speak one of these three languages, other accommodations may be incorporated, including allowing facilitated interviews by a relative or community representative speaking one of these three primary languages.

3.8.1 Special Issues in Recruiting Vietnamese Participants

To address issues around literacy, outreach, and access to the Vietnamese population, specifically, we will identify and work with NGOs having connections to, and understanding of, this community. For example, in analysis of the first ~30% of persons on the NIOSH roster (i.e., all that is available to date) and anecdotal reports from

persons in the field it appears that Vietnamese workers are substantially underrepresented on the NIOSH roster and may be similarly underrepresented on the PEC list relative to the general population. This may be due to language barriers that resulted in Vietnamese workers not receiving the worker training or completing the NIOSH roster. To help identify these workers and suitable controls, and to overcome language and cultural barriers to their participation in this study, we will work closely with community groups, enlisted via RFPs (and funded via subcontracts to the study contractor), that are integrated in the Vietnamese community/communities. These groups include Asian Americans for Change, Boat People SOS, Mary Queen of Vietnam Community Development Corporation, Vietnamese American Young Leaders Association of New Orleans, and Vietnamese Martyr's Church. We will meet with these community groups to explain the purpose of the study, the importance of participation of Vietnamese clean-up workers, the study methods, what will be expected of the participants, and how these groups can help us, and we will attempt to address their concerns.

For groups that agree to assist us in recruitment, we will work with their staff to develop strategies and resources that are both culturally and scientifically appropriate for promoting the study and identifying potential study participants. Ideally these groups will be asked not to recruit study participants *per se*, but rather to assist in developing interest and support for the study so that study staff can then approach potential participants in a methodologically rigorous manner. They may be asked to produce and provide to study investigators regularly updated lists of persons who they know or believe to have participated in oil spill clean-up activities, including names, telephone numbers, addresses, and other appropriate contact information (especially for any persons without telephones). They will be requested to provide some basic demographic information and reason for refusal for any workers who indicate that they are unwilling or unable to participate in this study. They will also be asked to provide similar lists of Vietnamese controls who are comparable to the clean-up workers they identify, based on criteria that they will develop together with study investigators. However, it may prove necessary to carry out a parallel supervised process to enroll this group, allowing subcontractors to conducting in-person screening interviews rather than telephone interviews. In that case, we will work with community groups to implement enrollment and data collection directly but provide sufficient oversight to ensure protocol standardization.

To minimize bias in subject selection and data collection, we will attempt to conduct all telephone interviews and in-home visits by study staff in Vietnamese. We will work with community group staff to approach persons who do not have telephones or other individuals recommended by the community group staff who could serve as liaisons. For persons for whom telephone interviews are not appropriate or possible, interviews and specimen collection will be conducted in-person, either at the subject's home or at another suitable location. While we will make every effort to provide Vietnamese-speaking phlebotomists/interviewers, it may be necessary in some cases to provide a trained Vietnamese translator with English-speaking phlebotomists/interviewers. Participants and those who decline to participate will be asked to provide names and contact information of any other Vietnamese clean-up workers they may know. In order to facilitate engagement, commitment, and valid data collection within this community, we will take the necessary steps to maintain as much transparency as possible including inviting community stakeholder groups to the interviewer training sessions and inviting them to assist in developing the training materials to ensure cultural competency among the study staff. We will review these procedures on an ongoing basis and modify them

as needed to achieve the dual goals of enumerating as fully as possible the workers and suitable controls in this community and recruiting and interviewing them in a scientifically rigorous manner.

3.8.2 Special Issues in Recruiting Creole-Speaking Persons

Anecdotal reports indicate that Creole-speaking persons in the Gulf have also been involved in clean-up activities. These persons are likely to be substantially underrepresented on the NIOSH, PEC, and other worker training lists because most of these trainings have been conducted only in English, Spanish, and Vietnamese. We have no information on how many such workers there were nor on what types of clean-up activities they were engaged in. To fill in these critical information gaps, we will issue RFPs to local community groups to help us enumerate these population(s). If we determine through these means that there are sufficient numbers of exposed workers in this population, we will work with community stakeholder groups to promote the study and help recruit the workers and appropriate controls from this population in a similar manner to that described above for the Vietnamese.

3.8.3 Special Issues in Recruiting Women

Women will be recruited into the cohort by the same eligibility and selection criteria as men. However, some additional sex-specific questions, focusing on menopausal status, reproductive history, and pregnancy status, will be included in the enrollment questionnaire. Potential sub-studies of women will be considered later, based on the number of women, their exposure profiles, and the numbers of outcomes of interest. Women included in the Active Cohort who are pregnant at the time of in-home exam and biospecimen collection will be asked to postpone participation until 3-months post-partum.

3.8.4 Special Issues in Persons with Reactive Airways Disease

We may consider focused sub-studies among persons identified with, or suspected to have reactive airways disease at enrollment. The timing and nature of these sub-studies will depend on the number of such persons identified during enrollment and will be described in more detail at a later date.

3.8.5 Other Special Populations

Other subgroups may be identified for add-on studies of **focused** hypotheses related to **specific** exposure**s** or health outcomes. These studies may be initiated by us or by extramural collaborators. Participants will be informed that such **add-on** studies may be possible and that separate informed consent to participate will be obtained.

3.9 Home Visit

By going to participants' homes rather than requiring that they make their own arrangements for specimen collection or visit a central location, we minimize their burden for study participation while maximizing the likelihood that we will be able to collect the desired study data, biospecimens, and environmental samples. Only

participants selected for the Active Follow-up Cohort will be scheduled for an in-home visit by a field staff member (i.e., a home visit agent or HVA). We will ensure that HVAs hired for this study have the necessary education, qualifications and experience to conduct the required home visit activities, or we will provide additional training as needed. Home visits will be scheduled seven days a week between the hours of 8 AM and 9 PM local time. Sunday visits will not be scheduled in communities for which this is considered socially unacceptable. We anticipate that the home visit will take 2-3 hours to complete.

During the home visit, the HVA will administer informed consent. The HVA will return this document and completed questionnaires to the study office by overnight carrier. Present plans are for biospecimens and environmental samples to be sent by priority overnight carrier to the central processing laboratory for additional processing and storage. Because commercial carriers do not operate on Sundays, we are investigating use of specialty couriers that can make these off-hour pick-ups and deliveries, but typically at a premium price. To reduce the time until processing and storage of biospecimens, we are exploring contracting with clinical specimen processing service providers such as Quest, which typically operate 7 days per week. In this alternative scenario, the HVA would deliver all specimens/samples immediately upon completion of a home visit to a local Patient Service Center, where the samples would be placed into the central laboratory's transportation network for prompt transfer to the central processing laboratory where the samples would undergo further processing and aliquotting. Even if using a clinical specimen processing service is determined to be feasible for this study, biospecimens for some participants, such as those in more remote areas not near a Patient Service Center, will still need to be shipped by priority overnight carrier to the central processing laboratory.

3.9.1 Advance Study Packet

In advance of the home visits, we will assemble and mail to each participant a home visit kit containing the following materials needed to conduct the visit:

- Appointment cover letter;
- Home visit preparation instruction sheet;
- FAQs;
- Informed consent form for the participant to review in advance;
- Work events calendar (to act as a memory aid in preparation for the questionnaires to be administered during the home visit);
- Phthalate/Bisphenol A free urine collection container and lid along with detailed instructions for collecting a first morning void;
- ID labels for participant -specific documents and specimens/samples.

The HVA will bring all other materials needed for the home visit.

3.9.2 In-Home Visit

At the beginning of the visit, the HVA will obtain informed consent prior to conducting any study procedures. Additional details concerning the informed consent procedure can be found in Section 10.2. After consent is obtained, the HVA will collect physiologic and anthropometric measures; biological specimens (e.g., blood, hair, nail, urine, etc.); environmental measures; and administer a baseline questionnaire data collection. The HVA will also determine and record the latitude and longitude of the home using a

handheld Global Positioning System (GPS) device; this information will be used in later GIS-based studies to determine residential proximity to sites of potentially relevant environmental exposures, such as petroleum refineries and toxic waste dumps and incinerators. If a subject is interviewed away from the home, their residential address will be collected (along with nearest cross-street and landmarks) so that it can be more accurately geocoded using existing software geocoding tools; this will also be done for previous addresses as indicated in the subjects residential history. Table 1 provides an overview and approximate timeline of the home visit activities.

Table 1. Home Visit Overview

Activity	Time	Notes
Interview is assigned to HVA, and HVA calls participant to schedule in-home visit	N/A	Scheduled at least 3-5 days in advance. Provide toll free number and website to reschedule if necessary
Mail Home Visit Kit	N/A	Packet arrives 3-5 days in advance of scheduled home visit
First morning void urine collection*	N/A	Collected by the participant using urine collection kit provided
Arrival, greeting and set-up	5 minutes	
Informed consent	15 minutes	Review and obtain informed consent
Anthropometric / Physiologic measures collection	20 minutes	Ht, Wt, BP, Waist and Hip Circumference, Spirometry
Biological specimen collection and labeling	20 minutes	Hair, Nail, Blood, Toenail Clippings
Questionnaire measures collection	60 minutes	
Environmental sample collection and labeling	10 minutes	Tap water, Dust wipe
Biological specimen processing and labeling	10 minutes†	

Activity	Time	Notes
Clean-up and packing	10 minutes	
Departure	**Total time:** 2 hours, 30 minutes	
Post-visit processing		Shipping and data back-up

** If first morning void collection has not been obtained when the study staff arrive, the HVA will request that the participant provide a random or "spot" urine during the home visit instead.*
† Blood will be allowed to clot for at least 30 minutes while the baseline questionnaire is being administered to the study participant and will be centrifuged for 15 minutes following the questionnaire administration (and during the environmental sample collection) in order to minimize the biospecimen processing time and overall time spent in the home during this visit.

3.9.3 Baseline Questionnaire

The baseline questionnaire is coordinated with the telephone enrollment questionnaire to ensure that adequate exposure and covariate information is collected from all study participants. The baseline questionnaire to the active follow-up cohort obtains more details on items such as residential and occupational history, personal and family medical history, alcohol and tobacco consumption, mental health and anxiety, etc.

Before designing the questionnaires, study investigators referred to questionnaires used by other data collection efforts occurring in the Gulf States, regionally, and nationally in order to facilitate regional and national comparisons and potential cross-study analyses. National studies such as the NHANES, BRFSS, and NSDUH were used. We also referred to measures provided in the PhenX Toolkit as the basis for our questionnaire modules. We substituted sections from other questionnaires when we found something that appeared to work better or to better capture our study interests.

Questionnaires are organized into a modular format and collect information on oil spill clean-up related activities (in the telephone enrollment questionnaire completed by all participants); residential history; personal and family medical history; occupational history; reproductive history; demographic and socioeconomic factors; alcohol consumption; mental health status; a neurocognitive screener; and other information, including hobbies, sleep patterns, tobacco use, and consumption of seafood from the Gulf of Mexico. Although the interview asks for identifying information from the participant to facilitate follow-up and future linkage with external databases for GIS-based studies, the computer-assisted interview will be programmed to create a separate data file for identifying information in order to maintain a secure data system.

In developing our questions on environmental and occupational exposures, we first considered the chemicals that have been identified in the crude oil and also in the dispersants as identified by the National Toxicology Program (NTP). By linking to various national databases, we will be able to identify the potential toxicity of these agents. We also considered the frequency with which participants were engaged in oil-spill clean-up related activities and their past occupational and recreational exposures to these agents.

The questionnaires focus on time periods before, during and after each participant's clean-up related activities to get a full accounting of potential exposures to these chemicals. A work events calendar will be provided to the participant in advance of the study visit to facilitate recall of their clean-up related activities. In order to improve exposure classification based on self-reported histories, we will use a series of job modules that focus more directly on specific activities and exposures in past jobs with potential for relevant exposures.

3.9.4 Anthropometric/Physiological Measures

The HVA will weigh (kg) participants and measure height (m), hip and waist circumference (cm), and take the participant's heart rate and blood pressure. Height (m) and weight (kg) will be measured using a metal tape measure and digital scale using standard methods from the NHANES IV national survey. All measurements will be taken three times. For blood pressure we will alternate left and right arm. If a person is unable to stand, we will measure waist circumference and sitting height using the crown to rump method with a cloth tape measure, but we will not measure their weight. We will use a cloth tape measure to collect waist circumference. We will provide participants with a report of their anthropometric measures during the field visit. To reduce the amount of equipment needed and facilitate training and scheduling, we plan to perform pulmonary function testing during the home visit on members of the Active Follow-up Cohort who live within the immediately affected areas, which represents approximately 75% of the members of this cohort.

3.9.4.1 Heart Rate and Blood Pressure Measurement

Three blood pressure and heart rate measurements will be collected by trained study staff. Heart rate will always be measured prior to respiratory testing. If a person's resting heart rate is > 120 beats/minute, they will be excluded from participating in the respiratory testing. Blood pressure will be measured three times using standard clinical equipment and these results will be provided to the participant at the home visit along with information regarding what these blood pressure results mean using a form similar to that being used in the NIEHS Sister Study. Seated heart rate and blood pressure will be taken three times in rapid succession after a 5 minute rest period.

3.9.4.2 Pulmonary Function Testing

Pulmonary function testing (PFT) will consist of spirometry data collection. All PFT will be conducted using American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [Pellegrino, et al. 2005].

The PFT will be performed using a portable, battery operated, ultrasound transit-time based spirometer (EasyOne; NDD Medical Technologies, Chelmsford MA, USA, or a comparable model). A full FVC maneuver will be used. We will obtain three ATS acceptable forced expiratory maneuvers out of a maximum of eight attempts. All spirometry examinations will be done with the person seated and wearing a disposable nose clip. We will use new individually packaged, disposable mouthpieces for each subject and a new spacer for each subject.

Combined with the symptom and medical history information, this objective measure of respiratory status will allow for an assessment of obstructive lung disease. By detecting these small changes in pulmonary function in the population as a whole, we will be able

to make comparisons to other environmental exposures including air pollution and environmental tobacco smoke in order to assess the potential severity of their disease.

To the extent possible, we will ask participants to withhold their asthma inhalers on the day of the examination (a commonly used protocol). For those participants unwilling or unable to withhold medications, we will document this during the home visit. For all participants, we will record the timing and dosage of all asthma medications over the preceding seven days.

To ensure quality results, we will conduct formal training and recertification on all field procedures. The HVA will be required to take a NIOSH-approved spirometry course, which is a well recognized training among medical professionals. In addition, all HVAs will complete the online exam and submit 10 practice tests administered by Hankinson Consulting, Inc (Athens, GA, USA). All spirometers will undergo standard quality checks before use in the field. To ensure high quality control and HVA feedback, we will use the reviewing software recently developed specifically for the EasyOne spirometer by Hankinson Consulting, Inc (Athens, GA). An expert in pulmonary function quality control will review all tracings on a weekly basis and override any software-provided readings if needed. The quality scores and other results will be electronically forwarded to field coordinators who will feed the quality information to the HVAs. If an unexpected number of unacceptable tracings occur, the HVA in question will be retrained.

Participants who answer yes to any of the following questions will not undergo spirometry during the visit:

- In the past three months, have you had any surgery to your chest or abdomen?
- In the past three months, have you had a heart attack or stroke?
- In the past three months, have you had a detached retina or have you had eye surgery?
- In the past three months, have you been hospitalized for any other heart problem?
- Are you pregnant?
- Are you currently taking medication for tuberculosis?

Additionally, if a participants resting heart rate is >120 beats/minute, they will be excluded from PFT.

Our exclusion questions include all of those used in BOLD [Buist, et al. 2007] and PLATINO [Menezes, et al. 2005], multinational studies that enrolled over 14,000 adults over age 40 years for pre and post bronchodilator spirometry with only trained technicians. No adverse events occurred in either the BOLD or PLATINO studies. These exclusions are considered very conservative and these questions are not generally

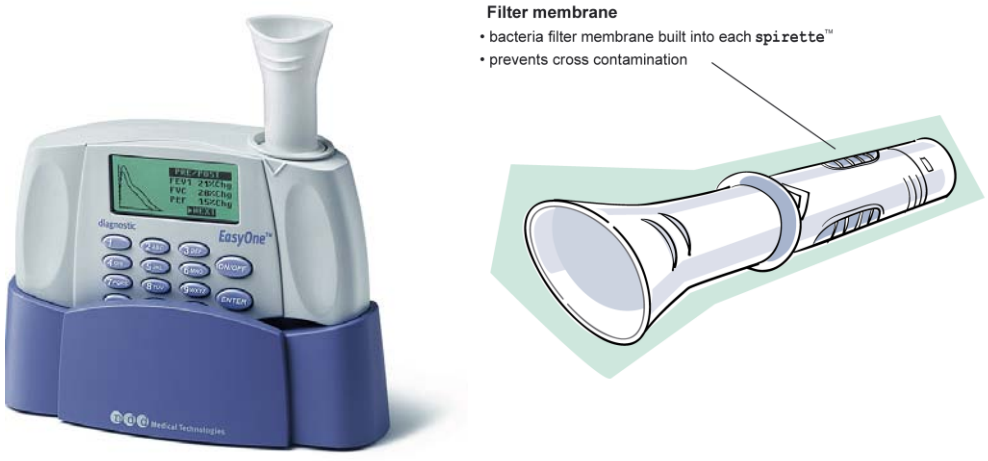


Figure 1. Example of EasyOne Spirometer and Disposable Mouthpiece

asked before spirometry is done in clinical practice.

3.9.5 Collection of Biological Samples

Biological specimens will be collected from participants in their homes by a trained HVA. The HVA will draw blood, retrieve urine specimens, and direct the participant to collect hair and nail samples. The following specimens will be collected:

- **Blood samples**: The HVA will collect 52.5 mL of venous blood into eight Vacutainer tubes:
  - *Lavender Top EDTA Tubes*: Three purple-topped tubes will be collected:
    - One 10 mL and one 6 mL tube will provide plasma, buffy coat, and RBCs for future analyses.
    - One 2 mL tube will either be 1) analyzed for CBC with WBC differentials upon arrival in the central laboratory for persons tagged to be part of the Biomedical Surveillance Sub-cohort or 2) processed for plasma, buffy coat, and RBCs for future analyses for the rest of the Active Follow-up Cohort.
  - *Royal Blue Top EDTA Tube*: One 6 mL trace metals tube will frozen for future measurement of As, Ca, Cd, Cr, Cu, Fe, Mg, Mn, Pb, Sb, and/or Zn.
  - *Red Top Serum Tube*: Two 10 mL tubes with no additives will provide serum and clots, which will be frozen for future analyses.
  - *Yellow Top ACD-B Tube*: One 6 mL tube with Acid/Citrate/Dextrose Solution B tube will be collected from each participant for future analyses. How the specimen is processed will depend on whether the participant is a member of the Biomedical Surveillance Sub-cohort, as described below.
  - *PAXgene RNA Tube*: One 2.5 mL PAXgene blood RNA tube will provide stabilized whole blood for mRNA isolation for future analyses.

- **Urine**: Each participant will be asked to collect a first morning void urine sample on the day of the scheduled visit in the phthalate/BpA-free collection container from the Home Visit Kit. If a FMV was not collected, the HVA will ask the participant to provide a "spot" urine. A portion of the specimen will used for a basic chemistry urinalysis (by dipstick) to measure protein, glucose, and several other parameters. The remainder of the urine sample will be processed in the Central Processing Laboratory for storage as described in Section 3.11 and as illustrated in Appendix C2.
- **Toenails**: The HVA will ask each participant to collect toenail clippings from each toe unless they have a medical or physical condition (e.g., diabetes) that would prohibit collection. Toenails will be stored under controlled ambient temperature and humidity for future analysis of metals.
- **Hair**: Each participant will be ask to collect a small hair sample as close to their scalp as possible. Hair will be clipped to indicate which end is closest to the scalp and stored in a manila packing envelope at room temperature for future analysis of metals and cortisol.

Saliva: All study participants who are unwilling or unable to provide a blood sample during the home visit will subsequently be mailed an Oragene OG-250 DNA Self-Collection kit, together with instructions for using and returning the kit, and a stamped, self-addressed padded envelope for returning the kit to the central processing lab. The CPL will store these samples as described in Section 3.11 and as illustrated in Appendix C.2.

3.9.6 Home Environment Sampling (tap water, dust sample)

The HVA will be trained to collect the following home environmental samples according to detailed sample collection protocols.

- **Tap Water**. The HVA will collect approximately 100 mL of home tap water sample into amber polyethylene container to protect the sample from light.
- **Household Dust**: The HVA will collect a household dust sample using a tared electrostatic dust wipe (e.g., the Swiffer™ Dusters, or a comparable model). The HVA will dust surfaces that may not frequently be dusted such as the tops of door sills or window sills, the tops of wall-hung picture frames, the tops of refrigerators, etc. The HVA will use the dust wipe to collect dust samples for approximately 5-10 minutes. The wipe will be shipped to the CPL along with the other biospecimens and tap water sample for further processing and storage as described in Section 3.11 and illustrated in Appendix C.

  Collecting household dust samples will enable a snapshot view of exposure to potential environmental confounders such as metals, pesticides, phthalates, and endotoxins. While other studies have collected samples using high power vacuum cleaners under a standard protocol, investigations have demonstrated good agreement between dust collected from household vacuum cleaner bags and the more industrial vacuum samples, typically considered the gold standard. In addition to greater cost, the collection and processing (or storage) of bulky vacuum cleaner bags presents logistical challenges and not everyone owns a vacuum cleaner or one with a bag. Studies such as the Agricultural Health Study and the Sister Study have used various techniques to collect samples of dust that settles onto household surfaces. The Sister Study piloted the ability of women to collect dust samples themselves using an alcohol-wipe approach, and with

Southwest Research Laboratories, have tested several brands for interferences with the chemicals of interest and to determine if pesticide and phthalates are detectable in homes.

The wipes will be available for future analysis to compare potential confounders such as pesticide and phthalate levels using alcohol wipes and vacuum cleaner bags to validate the suitability of our proposed approach for rank-ordering exposure levels. We will also test the feasibility of other methods to assess household exposures, including a dipstick test of nitrates in water, and a semi-permeable membrane being developed at the EPA for the detection of volatile compounds, and a small vacuum cleaner hose attachment that can be used with a variety of home vacuum cleaners to collect a small dust sample.

3.9.7 In-Home Biospecimen Processing and Shipment

After blood collection, the HVA will allow the blood in the serum tubes to clot for 25-30 minutes before centrifuging the tubes in the participant's home and separating the serum and clot, which will be retained. The HVA will then package all of the biospecimens and environmental samples for shipment to the CPL. The ACD-B tube and the 2 mL lavender top EDTA tube will be shipped at ambient temperature. The remaining specimens and environmental samples will be shipped cool but not frozen, accompanied by a frozen cold pack. These materials will be shipped by priority overnight service to the central processing laboratory. All biological samples will be shipped according to local, state, and federal requirements governing shipment of biological specimens.

If suitable arrangements can be made with a clinical specimen processing service, as described in section 3.9 above, then, after the serum is separated, specimens/samples for most participants will be promptly delivered to a local Patient Service Center for prompt transfer to the central processing laboratory, where the samples will undergo further processing and aliquotting.

3.10 Reports to Participants and Health Care Referrals

The HVA will give the study participant a brochure with contact information in case study participants have any questions or comments regarding their experience in the GuLF Worker's Study. They will be mailed a summary of their anthropometric and physiologic measures and selected biologic and environmental measures results along with information regarding normal ranges and instructions for contacting their physicians or other medical resource in their area should their results require immediate medical attention.

3.11 Laboratory Biospecimen Processing and Storage

Once the biospecimens have arrived in the Central Processing Laboratory they will undergo additional processing to separate out the various components (serum, plasma, cell fractions) and aliquoting of samples into small volumes for cryostorage, before being transferred to the long-term storage facility.

3.11.1 Central Laboratory Processing

Active Follow-Up Cohort Sample Processing: The aliquotted urine sample will undergo a dipstick urinalysis upon receipt. The three EDTA tubes will undergo

centrifugation to separate plasma, buffy coat, and RBCs, which will be aliquotted and stored in cryovials at -80°C. The ACD tube will be cryopreserved with 10% DMSO and aliquotted into cryovials, which will be subjected to programmed cryopreservation and stored at -80°C. The Trace Metal and PAXgene samples will be frozen in their original tubes at -20° C. The remaining urine, serum, blood clots, saliva, and water samples will be aliquotted into cryovials and stored at -20°C or -80°C, as appropriate. Cryovials for the urine samples will be phthalate/BPA-free. Dust, hair and nail samples will be maintained at ambient temperature and humidity.

Biomedical Surveillance Sub-cohort Sample Processing: Samples from this cohort will be processed the same as those of the rest of the Active Follow-up Cohort except that 1) The 2 mL EDTA tube collected during the baseline home exam will be analyzed for CBC with WBC differential promptly upon receipt at the central processing laboratory and 2) The ACD-B tube will be subjected to a discontinuous Percoll gradient separation procedure to isolate the lymphocytes (buffy coat). The lymphocytes will be mixed with 15% DMSO cryoprotectant, aliquotted, and subjected to programmed freezing as described above. The plasma and RBCs will be aliquotted into cryovials and stored at -80°C.

To minimize shipping expenses, the CPL will prepare the accumulated samples for shipment in bulk for archive storage at the NIEHS Repository.

3.11.2 Study Sample Long-Term Storage at the NIEHS Repository

Environmental Pathology Laboratories (EPL) is the contractor that operates the NIEHS Repository. EPL is located in Keystone Park, in close proximity to the NIEHS campus in the Research Triangle Park in North Carolina.

The EPL Repository is a state of the art storage facility which integrates structural, mechanical, electrical, HVAC, liquid nitrogen (LN2), and backup and monitoring systems to maintain ideal storage temperatures. These systems ensure specimen integrity and long-term preservation while supporting the safe and efficient storage of frozen specimens.

EPL's Repository houses a wide variety of biological and environmental samples and provides storage space for frozen, refrigerated, and room temperature specimens and associated data. The 17,000 square foot facility provides space for ultra-low temperature mechanical and liquid nitrogen freezers, data and specimen storage, and a processing laboratory. Nearly 10,500 square feet of space is dedicated to frozen storage, with a capacity of approximately 185 ultra-low temperature mechanical and liquid nitrogen freezers depending on the types of specimens to be stored. Additionally, the facility has three -20°C walk-in freezers totaling 675 square feet of space. Currently, EPL has over 3.5 million frozen specimens stored in archival storage.

EPL has over 25 years experience managing and operating archives and repository storage facilities for government and commercial clients. EPL provides qualified professional and technical personnel, materials, equipment and facilities for the receipt and long term, secure storage of samples, packaging of the samples for shipment, processing requests for samples and for aliquoting and labeling new samples, as well as distributing requested data and specimens.

Aliquots of a given type will be divided across liquid nitrogen and -20°C/-80°C mechanical freezers, as appropriate for each sample, to maximize integrity of the

samples during long-term storage and to reduce risk of complete loss due to freezer failure.

3.11.3 Analyses (including future studies)

Subjects targeted for the Biomedical Surveillance Sub-cohort (exposed and unexposed participants) will have their CBC and WBC differentials measured in the 2 mL lavender top tube promptly upon receipt of the tube by the central processing laboratory. This will allow assessment of these measures among many, if not all, workers with the highest expected benzene exposure (e.g., from exposure to crude oil or burning oil). These sets of samples will be flagged prior to shipping and the lab will be separately notified of these samples. The 2 mL lavender top tubes from all other subjects will be processed in the same manner as the other lavender top tubes. Future analyses performed on incoming fresh blood specimens in the sub-cohort may also include flow-cytometry to determine changes to specific cell populations, such as CD4 or CD8, CD17, and regulatory T-cells.

Immediately upon receipt of the urine samples at the central laboratory, a basic chemistry urinalysis (Multistix Pro 10LS reagent strips) will be performed to measure protein, creatinine, blood, leukocytes, nitrite, glucose, ketone, pH, and specific gravity.

All other samples will be processed and banked for future analyses.

Future analyses, to be conducted among targeted subsets of the cohort, include the alkaline comet assay and the micronucleus test on the cryopreserved lymphocytes to assess DNA damage; global hypomethylation and average telomere length in DNA from buffy coat; liver function tests (LFT) on serum; total immunoglobulins, autoantibodies, and inflammatory markers in the serum; antibodies indicating loss of latency of chronic infections such as Epstein-Barr virus and herpes viruses; gene expression related to exposure to benzene and other VOCs using the sample in the PAXgene tube; N-acetyl-beta-D-glucosaminidase (NAGs), beta-2 microglobulin, microalbuminuria, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein in the urine to assess kidney injury; polymorphisms in genes encoding metabolizing enzymes for benzene, other VOCs, and PAHs.

Exposure markers measured in stored specimens will include As, Cd, Cr, Mn, and Pb, in the whole blood (royal blue top tube); more distant exposure to metals in the toe nail clippings; cortisol and more distant exposure to metals in the hair; cortisol and urinary catecholamines in urine specimens.

If any workers are still engaged in clean-up or terminated clean-up within 30 days of enrollment in the cohort, we may also examine more transient markers of exposure, including urinary levels of benzene, toluene, mandelic acid, trans, trans-muconic acid, hippuric acid; and hemoglobin-PAH adducts.

3.12 Follow-Up of Cohorts

3.12.1 Telephone Questionnaires (Year 2 and 4)

Biennial follow-up of all active follow-up cohort participants will be conducted via telephone. In-person interviewing and web-based questionnaire options will be explored

as needed to increase response rates. These individuals will be asked to provide updates information on risk factors and outcomes that they have experienced since their last study interview. Additional follow-up questions can be developed based on the results of the baseline assessment. We plan on developing and seeking the necessary approvals for this questionnaire closer to the time of administration.

3.12.2 Biomedical Surveillance Sub-cohort Follow-up (Year 1 and 3)

Participants selected for the Biomedical Surveillance Sub-cohort will undergo more extensive testing and follow-up. These exams will be administered through an external contract or contracts run in collaboration with extramural collaborators. Detailed neurobehavioral, neurocognitive, and peripheral neuropathy measures will be collected. More thorough respiratory function testing, including bronchodilator challenge, will be performed. Additional tests and follow-up questionnaires and protocols will be determined with the extramural collaborators and necessary approvals will be obtained through the respective organizations.

3.12.3 Annual Morbidity and Mortality Outcomes (Year 2 and later)

Routine surveillance of GuLF study participants will be conducted beginning in 2. Follow-up will include linkage with State Cancer Registries and state vital statistics as well as linkage with the National Death Index (NDI). We will explore the feasibility of other passive monitoring for changes I health via linkage with other routinely collected surveillance data and electronic medical records that may become available.

Follow-up in Years 6-10

Routine surveillance of all GuLF study participants, using the NDI, existing syndromic surveillance databases, and state cancer registries (among others), will be conducted to investigate any morbidity and mortality associated with clean-up related activities.

Telephone interviews may be administered to all Active Follow-Up Cohort participants in Years 6-7 and 9-10, using questionnaires similar to those used in Years 2 and 4 (see 3.12.1 above), but possibly including additional questions based on the results of follow-up to date.

3.13 Retention Strategies

The strategies outlined in this section are intended to maximize retention, and in some cases recruitment, efforts. These strategies will capitalize on the community outreach effort as a core activity of the study design and implementation activities and build on the trust and rapport between the local members of the research team, the target communities and public health leadership across all five states.

A key to high response rates and long-term participation is not to simply contact participants when data are needed but rather to maintain contact in small ways and provide useful information including study results back to participants on a regular basis. We will provide regular feedback about study progress and group results as well as make sure we show our appreciation to the participants for their tremendous commitment to this study. We will also meet regularly as a study team to review progress made on retention efforts and obtain direct feedback to follow-up where necessary.

3.13.1 Annual Update of Contact Information

In order to minimize loss to follow-up, we will provide participants with contact information update forms that they can use to inform us of changes in their contact information. Update forms will be sent to participants once they have completed the interviews and home visit and will be included with all subsequent study mailings for use as needed. Thank you letters following the initial visit will include a GuLF Worker Study magnet that reminds participants to "keep in touch" and includes pertinent contact information. The study website will also feature an "update contact information" button on the homepage to register changes in contact information.

In addition, efforts will be made to update contact information annually. Participants will be asked to complete a one-page update form annually, whether or not they have had any changes in their contact information. Any mailings that have been "returned to sender" will undergo tracing to identify updated address information. These annual mailings will allow us to track changes in address and minimize losses-to-follow-up. We will send reminder post-cards to participants who do not return the annual follow-up form.

3.13.2 Newsletters and Other Mailings

Similar to the study website, annual newsletters will provide information on study progress and findings. Additionally, we will send birthday cards or holiday cards every year to enrolled participants along with small incentives/tokens of appreciation such as pens, notepads, calendars, and magnets with the study logo on them to maintain contact and long-term study interest.

3.13.3 Study Website

We will maintain a website to provide information about the study. The website will be updated regularly with details on recruitment efforts, study findings, and links to other organizations and information resources. Additionally, we will seek to have each of our community partners have a link on their website to the study website. As feasible, the website may contain details on upcoming or ongoing health research studies of oil spill workers. In order to support retention efforts, study participants will also be able to update their contact information on the website.

3.13.4 Social Media

Segments of the oil clean-up worker population are active social media users partly due to long trips away from home. Social media such as Facebook can be used to reach these workers to build study credibility, provide more frequent updates, and prompt participation in the out years of the study. However, as we expect web access to be quite incomplete, this approach is not expected to be effective across the cohort. As part of our retention efforts, we will explore the use of Web 2.0 resources (e.g. Facebook, Twitter, etc.) to encourage retention and facilitate follow-up. We will establish a presence on a site such as Facebook and maintain study updates as well as other information related to the spill. Study participants can opt to be emailed when updates are provided to the social media site or may even chose to be a "friend" of the site. Additionally, we will reach out to community organizations and invite them to be a

"friend" of the site. Because the social media landscape will undoubtedly change even during the 6-year study duration, we will continue to monitor for opportunities to utilize this technology for maintaining contact and encouraging retention in study activities. However, we must be assured that participant confidentiality will be maintained and that a significant proportion of participants are actively participating in these media to justify the feasibility to maintain these resources. We will seek IRB approval for all social media advertising activities.

3.13.5 Community Partnerships and Outreach

As described in Section 3.4 - Community Outreach, we will utilize linkages with the communities in all five states to augment recruitment efforts. Similarly, we will utilize community partnerships and relationships with other organizations to support retention efforts. First, we will continue to convene the Community Advisory Group (CAG) on at least a semi-annual basis throughout the life of the project. Subcommittees of the CAG may be created where necessary to address retention activities and other challenging situations regarding the cohort. We will rely on the leaders within each community to recommend retention strategies best utilized with their constituents. As we continue to develop relationships with communities, we will incorporate these strategies and revise the plans for study retention.

3.14 Remuneration

In addition to non-monetary incentives such as refrigerator magnets, chip clips, stationary and pens, participants will receive remuneration for their time and effort in the form of pre-paid gift cards. Remuneration will be offered at each stage of the study from the enrollment call and baseline home visit though each year of follow-up. The gift cards will be mailed to participants within 2 to 3 weeks of each completed study event. The amount of remuneration for each study event is provided in the table below. A separate remuneration schedule will be developed for the added more comprehensive activities of the Biomedical Surveillance Sub-cohort.

Table 2. Remuneration for Completion of Study Events by Cohort

Study Event	Active Cohort	Passive Cohort
Telephone Enrollment	$10	$10
Baseline Home Visit	$25	N/A
Year 2 Follow-Up Questionnaire	$10	N/A
Year 4 Follow-Up Questionnaire	$10	N/A
Total in first 5 years	$55	$10

3.15 Study Timeline

The GuLF Worker Study investigators will engage community and scientific leaders during the study design process for input and refinement. A timeline of study activities is presented in Table 3.

Table 3. Study timeline

	Q3 2010	Q4	Q1 2011	Q2	Q3	Q4	Q1 2012	Q2	Q3	Q4	Q1 2013	Q2	Q3	Q4	Q1 2014	Q2	Q3	Q4	Q1 2015	Q2	Q3	Q4
Study Design and Scientific Input	●	●																				
Community Outreach	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study Start		●																				
Subject Recruitment		●	●	●	●																	
Enrollment Questionnaires		●	●	●	●																	
Home Visits		●	●	●	●	●	●															
Biomedical Surveillance Sub-Cohort Follow-up						●	●	●	●					●	●	●	●					
Newsletter Follow-up						●	●	●	●					●	●	●	●					
Year 2 Follow-up										●	●	●	●									
Year 4 Follow-up																		●	●	●	●	

4 Evaluation of Benefits and Risks

4.1 Potential Benefits

All study participants may benefit from positive feeling associated with participating in a study of the health effects of the oil spill that may be of value to their community. In addition the knowledge gained from this study may have a significant impact on future public health responses to similar disasters. It is also possible that participants may benefit directly from public health responses that are based on early findings from this study.

Participants in the active cohort may benefit from receiving results of medical evaluations and health care referrals that they may not otherwise receive (see Section 3.10. - Reports to Participants and Health Care Referrals).

4.2 Potential Risks

The questionnaires and procedures in this observational study present minimal risks to study participants. The questionnaires are based on instruments that are widely used in epidemiological studies. Adverse events associated with study procedures are expected to be uncommon and limited to mild and transient discomforts. In order to minimize risks to participants, all study procedures will be conducted by qualified, experienced, and well-trained field staff.

The main risk in questionnaire administration involves questions about sensitive health topics or personal experiences that may be traumatic. Participants will be told that they can skip any questions that make them feel uncomfortable or end the interview at any time. Participants will also be warned of the possibility of loss of privacy should their de-identified data distributed through controlled access procedures (see section 11.2a) be linked back to them in ways that cannot be foreseen at present.

Pulmonary function testing is considered safe. The primary risk, which is exceedingly rare, is fainting in older participants with impaired lung function. We minimize the chance that this rare event will occur first through our very conservative exclusions for pulmonary function testing – any heart attack or hospitalization for other heart problem or stroke in the past 3 months. Pregnant women will not undergo pulmonary function testing until at least 3 months post-partum. To further minimize risk of fainting, pulmonary function testing is done in a seated position, and study staff are trained to look for signs of dizziness or other problems and to stop the maneuver if necessary. The risk of infection is all but eliminated by using disposable mouthpieces (spirettes). These disposable mouthpieces have the additional protection of having a built-in bacterial filter. In the PLATINO [Menezes, et al. 2005] and BOLD [Buist, et al. 2007] studies, home visits were conducted on 14,000 adults over age 40 by trained technicians only, without physicians present, and no adverse events were associated with in-home spirometry.

There may be some minor discomfort associated with blood collection, including temporary pain, bruising, or swelling at the phlebotomy site. Fainting during blood collection is exceeding rare.

There is also a remote risk of accidental disclosure of study information. Measures that will be taken to guard against accidental disclosures include maintaining complete confidentiality of the questionnaires and laboratory samples, use of secure data systems, and staff training (see Section 10.3 – Participant Confidentiality).

5 Adverse Event Reporting

Adverse events associated with are expected to occur very infrequently. Field staff will be trained to detect and respond to adverse events. They will also expect to promptly report clinically significant adverse events. The principal investigator will be responsible for reporting clinically significant adverse events to the IRB according to NIEHS policy.

6 Study Oversight

The Principal Investigator will monitor and evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of contractors and other factors that can affect study outcome. This monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

The study team, all of whom will contribute to study oversight, has the experience necessary to provide this oversight:

- Dale Sandler, Ph.D. Principal Investigator NIEHS
- Richard Kwok, Ph.D., Co-Investigator, NIEHS
- Lawrence Engel, Ph.D., Co-Investigator, Memorial Sloan-Kettering and NIEHS
- Aaron Blair, Ph.D., Co-Investigator, NCI
- Stephanie London, M.D., Dr.P.H., Associate Investigator, NIEHS
- Aubrey Miller, M.D., M.P.H. Associate Investigator, NIEHS
- Christine Parks, Ph.D., Associate Investigator, NIEHS

SRA International (SRA), a provider of professional research services, will provide support for this study through an existing contract with the NIEHS. SRA will oversee the day-to-day activities of the study with oversight from the NIEHS investigators. SRA will be responsible for hiring, training, and managing call center and field staff. SRA will ensure that all staff members have the proper education, experience, and training required for their role in the study. All staff will be trained on human subjects protections, the study protocol, and study procedures relevant to their role. They will also be required to sign confidentiality agreements. Whether SRA hires staff directly or subcontracts with a staffing agency, SRA will manage and oversee all study operations and training. SRA will also provide data management services and subcontract for lab processing services.

A GuLF Worker Study Scientific Advisory Board will be established as a subcommittee of the NIEHS Board of Scientific Counselors to provide additional oversight. This Board will include one or more members of the Board of Scientific Counselors, scientific experts, community representatives and Federal agency representatives. A separate Community Advisory Board, consisting of representatives of key study populations in the affected states, also will be established. Through funding made possible by a Gift to the NIH, the NIH has arranged to have the Institute of Medicine review the initial plans for

the study and monitor study progress. The IOM is scheduled to hold its first meeting focused on the GuLF Worker Study on September 22, 2010. It is expected that the IOM will meet twice a year for several years, and then annually to review study progress and findings. An Interagency working group made up of representatives from each Federal Agency involved in some aspect of the oil spill response met on August 19, and is also expected to meet regularly to provide study oversight. Continuity across committees and review groups will be provided by including some IOM members and some of the same Federal Agency representatives on the Study's Scientific Advisory Board.

7 Statistical Analysis Methods

7.1 Treatment of Exposure Status and Health Outcomes

Estimates of quantitative levels for specific exposures will be developed to the extent possible by the industrial hygiene team. Exposure status (e.g. any contact with crude oil, dispersants, or relevant crude oil specific chemicals, e.g., benzene, heavy metals, etc.) will also be defined dichotomously as "exposed" or "unexposed" based on the definitions given above for the study population and an activity-based exposure reconstruction (Sections 3.1.1 and 3.1.3). Similarly, health outcomes will be examined quantitatively where appropriate (e.g., FEV1/FCV, CBC measures), and will also be defined as "present" or "not present" based on the existence of specific endpoints within each disease area of interest (respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, renal, liver).

7.2 Statistical Methods to Address Study Objectives

The objectives of this study are to evaluate and characterize relationships between exposures to oil, oil byproducts and/or chemical dispersants, and stress associated with the disaster and short- and long-term health effects. General analysis methods to address these objectives are as follows:

- **Short-term Outcomes:** Acute- and short-term health effects that may have been incurred during or immediately following exposure will primarily be assessed during baseline data collection and in the immediate follow-up time-period. Relationships between exposures and these outcomes will be investigated at the most basic level by fitting regression models: logistic regression models for dichotomous outcomes to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure and least squares regression for continuous outcomes to estimate betas and standard errors (SEs) for each exposure. Relevant demographic variables (e.g., sex, age, race, SES indicators) and other exposures will be included in the regression models as covariates and effect modifiers. More refined analyses will incorporate specific characterizations of exposure, such as type of work performed, location, nature, and duration of exposure, protective equipment used, and ultimately a quantitative index of exposures developed by a panel of industrial hygienists and other exposure experts to reflect the risk factors of interest. Outcomes that will be evaluated include respiratory symptoms, nausea, headaches, dermatitis, depressive symptoms, anxiety, FEV1/FCV, CBC components, WBC differentials, DNA damage, etc.

- **Long-term Outcomes:** Long-term health effects that may be incurred in the years following the exposure will be assessed at regular intervals through follow-up by interview or linkage with disease/mortality registries. Relationships between exposures and dichotomous health outcomes will be investigated by fitting binomial repeated measures models to each outcome, using standard statistical software such as SAS Proc GENMOD. Exposure effects will be assessed via ORs for each observation period. Non-dichotomous outcome measures will be investigated using generalized linear models; appropriate transformations will be used to satisfy model assumptions. Relevant demographic variables (e.g., sex, age, race, SES indicators) and other exposures (including ongoing, repeated environmental variables where available) will be included in the repeated measures models as covariates. These outcomes will include cancer, neurological (neurocognitive, neurobehavioral, neurophysiological) deficits, cardiovascular injury, reproductive effects, persistence of early effects, among others.

Various refinements to these basic methods as well as these additional analyses will also be pursued:

- **Confounding and Effect Modification:** Potential confounders and effect modifiers will be introduced into the models to determine the extent to which they might influence any effect. Stratified analyses will also be used, as appropriate. Information on many of these factors will be obtained by interview, but others may come from analysis of biologic specimens.
- **Repeated measures**: Repeated measurements on individual components of long-term health outcomes (examples: reported numbers of days experiencing asthma symptoms, FEV1/FVC) will be investigated for association with exposure through repeated measures models, while introducing appropriate effect modifiers. In particular, pulmonary function measures provide objective data that complement less objective self-reported symptom data, but are typically quite variable. Results from other studies suggest that, at a given time point, we can expect to detect differences in FEV1 as low as 5% between subgroups of about 250 participants per group with 80% power. Analyses to compare larger subgroups, compare groups across multiple time points, detect changes over time, or investigate the FEV1/FVC ratio all involve more stable measures or comparisons and so will exhibit greater statistical power.
- Non-reversing binary prospective outcomes, such as incident diagnoses, will also be modeled using Cox proportional hazards models.

7.3 Interim and Safety Analyses

Adverse events associated with study procedures such as blood draws and pulmonary function testing are expected to be uncommon and limited to mild and transient discomforts. Such events will be monitored through interim reports. Interim reports will also be used to monitor parameters that characterize the conduct of the study, such as pace of recruitment, completeness of scheduled activities, time lags associated with data entry and laboratory testing, as well as QC reports for issues such as inter-observer variability and inter- and intra-laboratory variability. Study statisticians will develop these

and other reports. No early stopping rules are in place for this study since there is no treatment and no anticipated risk to participants. Analyses of short-term health outcomes will be conducted after completion of baseline visits. Other interim analyses may be conducted in a blinded fashion so as not to influence investigators or study staff with respect to the conduct or completion of the study.

7.4 Laboratory QA/QC Analyses

Laboratory QA/QC data will be reviewed for evidence of excessive variability and for trends indicating shifts in process control. Data from blind QC samples submitted to laboratories will be analyzed and within-pair coefficients of variation (CV) for internal (within laboratory) consistency samples will be calculated. Inter-laboratory reliability will be investigated by analysis of results of laboratory same-sample analyses. We will collect the full complement of blood and urine samples from up to 200 volunteers from outside the study population in order to create individual and pooled samples to be used for quality control purposes such as assessing long-term storage effects and assay batch variability.

7.5 Sample Size Considerations and Power

7.5.1 Estimated sizes of worker (exposed) and non-worker (unexposed) groups

Based on currently available information, we anticipate that when we merge the PEC list, the NIOSH list, the lists of workers from Federal agencies that may be included in this study (e.g., Coast Guard, Fish and Wildlife Service, US Geologic Survey), and other worker lists, and then remove duplicates, persons who provided no contact information, and persons who indicated that they intended to work on clean-up for less than one week (< 0.2% of the early NIOSH Roster, but possibly a larger number; likely to be persons with no intention of engaging in clean-up work), the merged list will contain approximately 80,000 names. Based on early NIOSH information, approximately 95% of these persons will be from one of the five Gulf States. Restriction of the workers, for logistical reasons, to persons from the five Gulf States and to those workers from outside of those states who experienced certain high exposures such as to benzene, burning oil, and dispersants will produce a list of approximately 77,500 persons, It is expected that loss to follow-up, non-response, and refusal will reduce this list to about 54,000 eligible persons (approximately a 70% participation rate). Among this group, we estimate that about 43,000 (80%) will have engaged in clean-up activities while the remaining 11,000 (~20%) did not.

Assuming an 80% participation rate, there are sufficient eligible persons to recruit 20,000 workers and 6,000 controls into the Active Follow-up Cohort. Based on current information, we estimate that about 26% of the controls are from outside the immediately affected communities. By oversampling these non-local controls, we expect to recruit approximately 2,000 non-local controls and 4,000 local controls, and will identify an additional 1,000 Federal controls from other sources.

The Passive Follow-up Cohort will include all persons who either were not invited to be part of the Active Follow-up Cohort because the target number for their job/exposure category had been reached or who refused to be part of the Active Follow-up Cohort (but

participated in the enrollment telephone interview). This represents about 23,000 workers and about 5,000 controls.

Thus, the total size of the full cohort is anticipated to be approximately 55,000 persons (43,000 workers and 12,000 controls), consisting of 27,000 in the Active Follow-up Cohort (20,000 workers and 7,000 controls [4,000 local and 2,000 non-local and 1,000 Federal]) and 28,000 in the Passive Follow-up Cohort (23,000 workers and 5,000 controls).

Based on other prospective observational studies, we anticipate 90% follow-up and participation in telephone interviews after enrollment for the Active Follow-up Cohort. Thus, completed follow-up interviews are expected for approximately 18,000 workers and 5,400 controls in Years 2 and 4.

7.5.2 Sample Power

This study is designed not around a few narrow *a priori* hypotheses, but rather to allow the investigation of a wide range of potential adverse health effects. The study size and the number of individuals who experienced a given exposure – and the consequent statistical power – have largely been determined by the number of individuals involved in the clean-up operations and their distribution by task/exposure. While this study will have limited power to examine certain rarer exposures or outcomes in the near future, this is the largest study to date of oil spill clean-up workers and it is important that we address, to the extent feasible, the wide range of public health concerns. It is a prospective study and as time passes, if the exposure continues to exert an impact on some health outcome, power will increase.

Table 3 presents minimum detectable odds ratios across a range of proportions of exposure among the workers and of health outcome among the controls. Estimates are shown separately for analyses of the full cohort and of the Active Follow-up Cohort, including all controls or including only the non-local controls. All estimates are based on a two-sided test with α=5% and power=80%. As the table shows, this study has excellent power to detect small risks, except when exposure or outcome is rare. For example, in an analysis of the full cohort, if 10% of the workers received a given exposure (e.g., high exposure to VOCs) and the incidence or prevalence of disease is 1%, this study would have sufficient power to detect an OR of at least 1.56 when using all 11,000 controls and 1.95 when using only the 2,500 non-local controls. In an analysis restricted to the Active Follow-up Cohort, with proportion of exposure of 10% and disease incidence/prevalence of 10%, the minimum detectable OR would be only 1.26-1.32 when using the full control group (N=6,000) or the non-local control group (N=2,000). For perspective, estimated relative risks of lower respiratory tract symptoms observed among clean-up workers in previous oil spills ranged from 1.5 to 3.6 [Janjua, et al. 2006, Zock, et al. 2007, Meo, et al. 2009, Sim, et al. 2010]. Thus GuLF Study is sufficiently powered to observe such relative risks for these outcomes.

Table 3. Minimum detectable odds ratios for a range of proportions of exposure among the workers and for all controls vs. non-local controls, based on a two-sided test with α=5% and power=80%

Size of control group (i.e., all vs.	**Proportion (N) of workers exposed to a given agent**					
	5%	**10%**	**25%**	**50%**	**75%**	**100%**

non-local)

Full cohort: 43,000 workers, 11,000 controls:

	N=2,150	N=4,300	N=10,750	N=21,500	N=32,250	N=43,000
Proportion of controls with outcome=1%						
11,000	1.75	1.56	1.42	1.36	1.34	1.33
2,500	2.02	1.86	1.76	1.72	1.71	1.70
Proportion of controls with outcome=10%						
11,000	1.23	1.18	1.13	1.11	1.11	1.10
2,500	1.30	1.25	1.22	1.21	1.21	1.21
Proportion of controls with outcome=30%						
11,000	1.15	1.12	1.09	1.07	1.07	1.07
2,500	1.19	1.16	1.14	1.14	1.14	1.13

Active Follow-up Cohort: 20,000 workers, 7,000 controls:

	N=1,000	N=2,000	N=5,000	N=10,000	N=15,000	N=20,000
Proportion of controls with outcome=1%						
6,000	2.14	1.84	1.62	1.52	1.49	1.47
2,000	2.38	2.12	1.93	1.86	1.83	1.82
Proportion of controls with outcome=10%						
6,000	1.35	1.26	1.19	1.16	1.15	1.15
2,000	1.40	1.32	1.27	1.25	1.24	1.24
Proportion of controls with outcome=30%						
6,000	1.23	1.17	1.12	1.10	1.10	1.09
2,000	1.26	1.21	1.17	1.16	1.16	1.15

Minimum detectable differences for continuous outcomes are presented in Table 4. Differences are expressed in standard deviations (SDs) and are based on a two-sided test with α=5% and power=80%. Results are shown separately for analyses of the full cohort and of the Active Follow-up Cohort including all controls or including only the non-local controls. This table demonstrates that the present study has sufficient power to detect small differences in continuous outcomes. For example, in an analysis of the full cohort that examines an exposure of 10% prevalence, we will be able to detect minimum differences of less than 0.050-0.071 SD. A similar analysis in the Active Follow-up Cohort will be able to detect minimum differences of less than 0.09 SD (0.072 when using all controls and 0.089 when using the non-local controls). For perspective, in a study of volunteers involved in the Prestige oil spill clean-up and unexposed controls [Laffon, et al. 2006], results of the comet assay in peripheral blood leukocytes showed differences between the two groups of approximately 4.3 SD in comet tail length. A study

of health effects related to the Tasman Spirit oil spill found a difference of about 0.6 SD in symptom scores between coastal residents affected by the spill and persons living away from the site of the spill [Janjua, et al. 2006]. The present study is very well powered to detect such effects.

Table 4. Minimum detectable differences, in standard deviations, for continuous outcomes for a range of proportions of exposure among the workers and for all controls vs. non-local controls, based on a two-sided test with α=5% and power=80%

Size of control group (full vs. non-local)	**Proportion of workers exposed to a given agent**					
	5%	**10%**	**25%**	**50%**	**75%**	**100%**
Full cohort: 43,000 workers, 11,000 controls:						
	N=2,150	N=4,300	N=10,750	N=21,500	N=32,250	N=43,000
11,000	0.066	0.050	0.038	0.033	0.031	0.030
2,500	0.082	0.071	0.062	0.059	0.058	0.058
Active Follow-up Cohort: 20,000 workers, 7,000 controls:						
	N=1,000	N=2,000	N=5,000	N=10,000	N=15,000	N=20,000
6,000	0.096	0.072	0.054	0.046	0.043	0.041
2,000	0.109	0.089	0.074	0.069	0.067	0.066

8 Analysis Plan

8.1 Primary Endpoints

Given the very limited health effects research conducted to date on oil spill clean-up workers, the GuLF Worker Study is designed not around a particular *a priori* hypothesis, but rather to allow investigation of a wide range of potential adverse health effects, including physical, psychological, and biological effects. These include both short-term and long-term effects focused on, but not limited to, the following areas: respiratory, cardiovascular, hematologic, dermatologic, neurologic, cancer, reproductive, mental health, immunologic, hepatic, and renal.

Questionnaire-based exposure information will be examined in relation to outcomes in both prospective and cross-sectional analyses in the full cohort or sub-cohorts. Because many biological and environmental assays are expensive and samples are limited, we also plan to carry out nested case-control or case-cohort studies within the cohort.

Many of the primary exposure measures will be from job-exposure matrices (JEMs), which will be developed by a panel of industrial hygienists using time-specific task and exposure data from a range of sources. These will be semi-quantitative (e.g., 5-point scale). They will be treated in statistical analyses as ordinal values or, depending on distribution or scientific considerations, collapsed into fewer categories (e.g., high vs. low).

Endpoints will be identified through several means. First, we will use the self-reported health information provided in the enrollment interview(s) to define case groups or to assign quantitative or semi-quantitative health categories for a given outcome or constellation of outcomes, as appropriate. Self-reported health histories from this interview will be used to identify outcomes with an onset or increase in severity after the subject began clean-up work (i.e., not a pre-existing condition). Some self-reported health information may be validated in sub-studies through subsequent information provided by the subject's doctor, the subject's medical record, and/or the subject him/herself. Second, we will have clinic information such as the FEV1/FVC results collected at enrollment from all subjects who live within the immediately affected areas and the urinalysis results obtained at enrollment from all subjects.

We will examine results of a Complete Blood Count (CBC) with white blood cell differentials among members of the Biomedical Surveillance Sub-cohort. Endpoints will include total WBCs, individual WBC components, red cell measures, and platelets. White blood cell and platelet counts have been found to be significantly reduced among workers with low exposure to benzene, with reduced hemoglobin concentration among workers with higher exposure to benzene [Lan, et al. 2004]. To explore potential effects of metals, particulates, and stress, we will examine measures of the acute phase response (C-reactive protein), inflammatory cytokines, as well as anti-nuclear and thyroid antibodies.

In subsets defined by higher or lower stress exposure and in vulnerable sub-populations, we will also examine antibodies to latent viral infections as indicators of sub-clinical depressed immunity. Antibodies to latent infections have been studied frequently in relation to the physiological impact of stress, and may vary according to socioeconomic factors [Aiello, et al. 2009, Dowd and Aiello 2009]. We will also examine stress-associated immunosenescence as indicated by average leukocyte telomere length and stress biomarkers [Epel, et al. 2004, Parks, et al. 2009], which along with viral antibodies may be related to a variety of chronic disease outcomes.

For a subset of subjects representing high and low exposures to agents known or suspected to be nephrotoxic, including volatile organic compounds and heavy metals, and also unexposed subjects, we will examine urinary markers of kidney injury, including N-acetyl-beta-D-glucosaminidase (NAGs), beta-2 microglobulin, microalbuminuria, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and liver-type fatty acid binding protein.

We will similarly conduct liver function tests using sera from a subset of subjects having either high or low exposures to agents known or suspected to alter liver function, including volatile organic compounds, PAHs, and heavy metals, and also unexposed subjects.

For a subset of subjects representing high and low exposures to agents known or suspected to be genotoxic, including volatile organic compounds, heavy metals, PAHs, and hydrogen sulfide, and also unexposed subjects, we will examine results of the comet assay and the micronucleus test. Comet assay measures will include the tail moment, defined as the product of the percentage of DNA in the comet tail and the tail length, and the tail intensity, defined as the percentage of DNA in the tail. Micronucleus test measures will consist of the frequency of micronuclei and the frequency of binucleated micronucleated cells.

During follow-up of the cohort, we will identify incident outcomes or changing severity of those outcomes via self-reported health status in follow-up interviews, via linkage with

cancer and vital status registries, and via testing of follow-up biospecimens. Our analyses will consider onset or changes in severity relative to both enrollment health status and health history, as appropriate. For some subjects, such as Coast Guard members, we may be able to obtain additional information from electronic medical records.

Continuous outcome measures such as FEV1/FVC will be treated as continuous and/or categorized according to appropriate cutpoints in statistical analyses. They will be log-transformed as needed.

Initial analyses will be largely descriptive, including examination of distributions of jobs, exposures, demographic and lifestyle factors, health history, and recent health outcomes at enrollment. We will quantify and examine patterns of missing data and outliers. We will perform data cleaning as appropriate. To the extent possible, we will explore potential bias in subject selection and reporting.

We will next conduct cross-sectional analyses, consisting primarily of comparisons of prevalence or extent of a given outcome by clean-up task or estimated exposure to a given factor (from the JEM). These will be performed using least squares regression for continuous outcomes or logistic regression for dichotomous outcomes, adjusted for confounders as appropriate. We will explore possible modifiers of effect such as race, sex, baseline health characteristics, lifestyle factors, and access to health care by also conducting stratified analyses by these factors, as appropriate and as numbers permit.

When follow-up data become available, we will also be able to perform prospective analyses linking clean-up activities/exposures to incident outcomes using Cox proportional hazards regression. We will use logistic regression for nested case-control analyses. Extent of change of outcomes will be assessed using least squares regression. Confounding and effect modification will be addressed as described above.

Clinical protocols for a number of outcomes, including respiratory and neurologic effects, will be developed and carried out in collaboration with local university partners identified through a request for proposals (RFP). Therefore, analysis of these outcomes will be addressed in a later protocol.

9 Training, Quality Control, and Quality Assurance

9.1 Staff Recruitment and Enrollment Process

9.1.1 Telephone Interviewers

Locating and screening tasks will be conducted by approximately 50 trained telephone interviewers working part time over different shifts. Interview staff are given training on good practices in interviewing—locating, gaining cooperation, overcoming barriers to participation and correctly coding outcomes, and American Association for Public Opinion Research (AAPOR) code of ethics which includes training on confidentiality and non-disclosure. Trainees also receive interactive cultural competence training. Administrative aspects of the computer-assisted telephone interviewing (CATI) system and time record keeping are practiced.

The training program will be tailored to meet the specific needs of this study, including successful approaches for conducting interviews with people facing the continuing life

disruptions following Rita/Katrina and now the BP oil spill. Interviewers will learn the best methods for refusal avoidance and conversion techniques, and will receive extensive hands-on training with the Computer-Assisted Interviewing (CAI) questionnaire. They will also learn the most effective ways to explain the importance of participating in the study, and how to best answer questions about the study's purpose and process. Interviewers will be trained to make respondents aware of other sources of information about the study, such as the website. Training will include sensitivity exercises designed to ensure that interviewers show unconditional positive regard for participants. Interviewers will be trained to use positive rather than patronizing language, use structured probes, check for respondent fatigue, and offer unbiasing encouragement. The training will focus on the three general challenges in interviews—communication,

Confidentiality safeguards will be maintained throughout the data collection period. All study personnel will be trained in their responsibilities under HIPAA to protect the confidentiality and privacy of each participant's personal health information and the civil and criminal penalties if they violate a participant's right to privacy. All interviewing staff will sign a Confidentiality Agreement and an Affidavit of Nondisclosure as part of their training on protecting the privacy and rights of respondents. Training will also include identification of social and mental health issues on need of intervention and appropriate protocols for seeking outside support or making community referrals.

9.1.2 Home Visit Personnel

Approximately 140 home visit personnel will be needed, as well as 14 field supervisors to collect clinical data and conduct the baseline interview. In this study, it is important to retain clinical interviewers with particular aptitude, skill, and sensitivity in working with persons having experienced natural disaster, life disruption, and probable dislocation.

Training for home visit data collection will start with a one-day field supervisor training prior to the clinical specialist (CS) training. This training will focus on data collection procedures, management of CSs, the importance of data quality and cost containment, and reporting. Following the field supervisor training, a two-day training sessions will be held for the CSs. The field data collection trainings will be conducted centrally. The training agenda will consist of large-group exercises, demonstrations, round -robin and dyad mock interviews, and question-and-answer sessions. CSs will be trained and tested on their mastery of the ethics and protection of human subjects in research, establishing rapport, setting visit dates, administering informed consent, and CAPI instrument use. They will also be trained in the clinical portion of the study protocol and tested specifically on the clinical protocol components to include setup, preparation and shipping of biological samples. The last day of training will be dedicated to practice. The CS will practice the complete baseline protocol under the close supervision of the field supervisors and trainers.

Periodically, field supervisors will accompany the CS for follow-up assessment of performance. Deviations from protocol evidenced in the receipt of data or specimens will be reported to the project and the relevant field supervisor who will follow-up with corrective training or dismissal of the CS. Standardization of Field Procedures

9.2 Data Quality Control

9.2.1 Data Collection Quality Control

At the core of our data collection efforts we will use the SPSS Dimensions Platform of survey support tools, built on open, standard technologies. The Dimensions platform has the following features:

A flexible interface for loading complex sample data initiates and drives study recruitment activities.

A Computer-Assisted Telephone Interview (CATI) component that guides project personnel through the interview process to determine eligibility. This component provides complex branching and algorithm support to collect data, make eligibility determinations, schedule future contact and direct the management of the new recruit's case to regional field supervisors. The CATI system allows data managers to monitor the recruitment process and all call center operations and success metrics. All CATI data are updated and managed in the central data management system. A notification system text-messages all receiving field representatives and managers when new cases are assigned to them.

A CAPI component running on field laptop computers to administer study questionnaires and capture clinical evaluations. The CAPI component guides field personnel through a questionnaire that has complex and conditional branching as well as rostering. The CAPI system provides real-time data validation, ensuring data are valid when captured and the immediate correction of data after an error is detected.

A central management tool that ensures that all CAPI and CATI data are collected into a single repository. The SPSS mrInterview tool manages the aggregation of laptop interview data. Field representatives connect to the communications portal (described below) using internet SSL technology, and automatically upload collected interview data and download preparatory data for forthcoming interviews. CATI user data are managed via the same SPSS tool that reads and writes data directly to the database.

9.2.2 Data Storage

All study data are housed in a single SQL Server data repository stored in the secure data center. This single database ensures that all system users are accessing the same database; allows for greater control via role-based access privileges; provides a robust architecture to support backup, security, and disaster recovery; and provides the flexibility needed to change the data input mechanisms that could change during a potentially very long study.

9.2.3 Data Management & Communications

The communications portal provides a single access point for all study data, reports, status updates and communications. The communications portal provides the ability to record, track, and analyze information associated with all types of case management activities such as scheduling, field interviews, tracking, and data acquisition. Project field personnel and other authorized project personnel connect to the communications portal over the Internet, go through an authorization process to establish an SSL connection,

and have access to a variety of functions that support their work. These functions include the ability to:

- Upload and download interview data
- Update interview schedules; view upcoming workloads for self or field staff (for supervisors)
- View data completeness reports including status of lab data
- Receive updates from project management including updated modules, with training provided
- Transmit laboratory data, receive validations
- Report and track errors or technical support needs and follow them to closure
- Receive warnings about overdue lab data transfers
- Update participant profile information if within user rights
- Keep track of project personnel; review training completeness reports and training records
- Monitor call center performance

Field representatives or managers connect to the DMS using laptops over the Internet or using smart phone tethering technology to gain Internet access. The DMS is integrated with email, enabling key events to trigger emails accessible via smart phones, ensuring that our distributed workforce is as current with information as possible. Regular data transmissions are required of all field personnel and phone email messaging prompt field staff to establish a data upload session if overdue.

The communication portal is key to the success of this project as it provides the most timely, accurate information and delivers it to project staff in real-time. For example, it is crucial that supervisors monitor recruitment and enrollment trends, and compare these results against various call center operations to improve overall recruitment success rates. Furthermore, enrollment success measures are compared based on time of day, call center operators, source of telephone number, and ordinal number of call attempts in order to identify trends that suggest necessary modifications.

9.3 Laboratory Procedures

9.3.1 Laboratory Data Quality Control

The study laboratories have been evaluated in part based upon their existing measures to assure the quality of their testing results. This includes (1) internal and external quality control and proficiency testing programs, (2) testing methodologies *vis a vis* industry standards such as those published by the Clinical Laboratory Standard Institute (CLSI) and the American Industrial Hygiene Association, (3) assay standardization to ensure the desired analytical range and sensitivity/specificity, and (4) methodology validation and analytical instrument performance using CLSI standard GP-31A and others, and pre- and post-analytical processes such as specimen receipt and accessioning, sample

aliquoting and batching, treatment of out-of-range results, reporting, and electronic data transfer.

A continuing performance review on both external and internal quality control programs will be conducted prior to commencing study data collection. Once home visits have begun and biospecimens and environmental specimens are submitted for analyses, test reproducibility and accuracy will be monitored as follows:

- *Assay Variability/Reproducibility:* Intra-assay (measurement) variability will be assessed through replicate assays conducted on the same day and in the same run. Inter-assay variability will be assessed through replicate assays conducted on different days in different runs.
- *Testing Accuracy:* Assessing the accuracy of test results presumes that there are available "gold standards" for each analyte of interest. While it is possible to quantitatively determine the amount of some analytes present (generally chemical compounds such as cotinine, lead, BFRs, and phthalates), definitively quantifying biological analytes such as IgE allergens, endotoxins, mold, and fungi, or volatile analytes such as formaldehyde and VOCs is more problematic and assay dependent. Biospecimen controls, environmental controls, and split specimens will be implemented for this purpose.

Laboratory testing quality will also be monitored by requiring submission of regular QC results as well as periodic proficiency testing program results. Modifications to testing procedures or sample processing/ extraction procedures will be avoided or minimized to the extent possible.

9.4 Mini-pilot for Overall Study

Study personnel, procedures and forms will need to be piloted in order to determine whether planned data collection efforts will yield valid and reliable results in the most time and cost efficient manner. We plan to conduct a mini-pilot study lasting 2-3 weeks in one focused geographic location within the study area to test all protocols and questionnaires in the study to ensure that the GuLF Worker Study data collection efforts will work as planned. Any necessary alterations in the study protocol that will need to be made can be identified and adjudicated accordingly based on the results of the mini-pilot.

10 Human Subjects Protections

10.1 Institutional Review Board

The investigator will submit the protocol, informed consent form, questionnaires, proposed recruitment materials, and other materials for participants to the NIEHS IRB for review and approval. Subjects will not be enrolled until the submission has been approved in writing by the IRB chair. Once the protocol is approved, the principal investigator will be responsible for obtaining IRB approval during annual Continuing Review for the duration of the study.

The principal investigator will submit and obtain approval from the IRB for all amendments to the protocol, informed consent form, and other study documentation referenced above. Amendments will not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to participants. The principal investigator will report adverse events, protocol deviations, inadvertent loss or disclosure of data, and loss of samples in accordance with IRB policies.

10.2 Informed Consent Process

Informed consent is an ongoing, interactive process that is initiated when the discussion regarding study participation begins and continues throughout the study. The consent process will begin with a lead letter and study brochure that provides and overview of the study and what it means to participate. During the telephone enrollment call, recruiters will explain the reason for the call, reference the lead letter and brochure that were sent by mail in advance of the call, introduce the study, and seek verbal consent for the initial screening and enrollment process. Participants will be informed that they will receive an annual Newsletter for the duration of the study and be asked to provide periodic contact information updates. The elements of passive follow-up via linkage with Cancer Registries, Vital Statistics and other data sources will be described and verbal consent will be obtained. They will also be informed about data sharing policies and that they may be contacted for potential participation in related studies but that they would have an opportunity to consent or not consent at that time.

Those who are interested and eligible for participation in the active cohort will receive additional information about the study and will be invited to schedule a home visit. Field staff will obtain written informed consent from participants prior to conducting any study activities during the home visit. In order to ensure that participants make an informed decision about enrollment, field staff will review the study's purpose, procedures, risks, and benefits, as well as the rights of research participants. Explicit consent will be sought for sharing individual-level data with qualified researchers committing to maintain participant confidentiality and comply with their consent provisions, similar to NIH policies for data sharing in genome-wide association studies (http://grants.nih.gov/grants/gwas/).

Field staff will allow the participant ample time to review the consent, ask questions, and obtain clarifications regarding the study prior to agreeing to enrollment. After voluntarily agreeing to take part in the study, participants will be asked to sign and date a current IRB-approved informed consent form. Field staff will return the signed consent to SRA for storage in the central study file. A copy of the consent form will be provided to the subject.

The consent form will contain contact information (i.e., toll-free phone number) for study staff that will be available to answer questions that may arise after the visit. Questions about study participation will also be addressed at the time of follow-up interviews.

Participants in the passive cohort will receive an enrollment packet after the enrollment call is completed. The packet will contain information that describes the study and provides contact information for study staff, including the toll-free study phone number and address for the study website. They will receive a description of what they agreed to during the telephone call and will be provided with information on how to withdraw from the study if they have changed their mind about long-term passive participation.

All participants will receive an annual newsletter that contains updates about study progress and findings (see Section 3.L.ii – Newsletters).

10.3 Participant Confidentiality

All study personnel will be required to complete on-line training in the protection of human research subjects. The investigators and study staff will strictly maintain participant confidentiality. This confidentiality will be extended to cover questionnaire data, clinical assessments, biological samples, and environmental samples.

All study-related information will be stored securely. All study datasets, laboratory specimens, and administrative forms will be identified by a coded number in order to maintain participant confidentiality. All records that contain names or other personal identifiers will be stored separately from study records identified by code number. All databases will be secured behind firewalls with password-protected access systems. Worksheets, lists, logbooks, appointment books, and any other documents that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

A Federal Certificate of Confidentiality will be obtained for this study. The Certificate will help protect against disclosures of study-related information by Federal, State or local civil, criminal, administrative, legislative, or other proceedings. Participants will be informed about the certificate during the informed consent process.

10.4 Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. Participants will be informed that unless explicit written instructions are received, investigators will continue to use data and samples collected up to the point of withdrawal although no new information will be collected from them. Study staff will seek feedback from the participant to determine reasons for discontinuation and to identify any barriers that can be addressed to keep the participant in the study. The reasons for all discontinuations will be recorded in the data collection system and routinely monitored by the investigators. Common barriers to ongoing participation may be addressed by changes in retention strategies or study design.

11 Data Handling and Record Keeping

11.1 Data Capture Methods

The core of the data capture system will rely on an industry standard field data collection system, using standard technologies. The system platform must allow for:

- A flexible interface for loading complex sample data initiates and drives study recruitment activities.
- A Computer-Assisted Telephone Interview (CATI) component that guides project personnel through the interview process to determine eligibility. This component provides complex branching and algorithm support to collect data, make eligibility determinations, schedule future contact and direct the management of the new

recruit's case to regional field supervisors. The CATI system allows data managers to monitor the recruitment process and all call center operations and success metrics. All CATI data are updated and managed in the central data management system. A notification system alerts all receiving field representatives and managers when new cases are assigned to them.

- A Computer-Assisted Personal Interview (CAPI) component running on field laptop computers to administer study questionnaires and capture clinical evaluations. The CAPI component guides field personnel through a questionnaire that has complex and conditional branching as well as rostering. The CAPI system provides real-time data validation, ensuring data are valid when captured and the immediate correction of data after an error is detected. SRA will prepare all CAPI systems, ship them to kickoff training, train personnel to use the system, and support the laptop PCs and CAPI applications via a toll-free and email helpdesk function.
- A central management tool that ensures that all CAPI and CATI data are collected into a single repository. The centralized data management and aggregation tool will manage the matriculation of data from field interview data platforms to the centralized data repository. Field representatives will connect to the communications portal (described below) using internet SSL technology, and automatically upload collected interview data and download preparatory data for forthcoming interviews.

11.2 Data Management Responsibilities

The captured data will be stored in a comprehensive data management system (DMS) that centralizes study information into an integrated solution. From the time that participants become part of the potential sample to the time they are complete, all project data are managed and tracked in the DMS. Project personnel will have an appropriate "view" into the data using role-based access control. The DMS will support the full scope of study data management activities, including management of study sampling; collection of field and laboratory data; management of participant activities (case management); reporting of all data collection efforts and status; and preparation of analysis datasets.

The heart of the DMS will be the database server. The database server will be configured for 24/7 operation, and provide the capability of offsite backups.

The DMS also includes a communications portal which provides a single access point for all study data, reports, status updates and communications. The communications portal serves as the gateway between users and the data repository. The portal enables the ability to record, track, and analyze information associated with all types of case management activities such as scheduling, field interviews, tracking, and data acquisition. Project field personnel and other authorized project personnel connect to the communications portal over the Internet, go through an authorization process to establish an SSL connection, and have access to a variety of functions that support their work. These functions include the ability to:

- Upload and download interview data

- Update interview schedules; view upcoming workloads for self or field staff (for supervisors)
- View data completeness reports including status of lab data and abstracted medical records
- Receive updates from project management including updated modules, with training provided
- Transmit laboratory data, receive validations
- Report and track errors or technical support needs and follow them to closure
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11.3 Data Access and Sharing

Given the public health importance of research on the health effects of the Deepwater Horizon disaster and its aftermath, results from the GuLF Worker Study will be made available for research use by any interested and qualified investigator or organization, within the limits of providing appropriate protection of research participants and compliance with their informed consent. Policies for data access will build on NIH established policies for controlled access to individual-level data in genome-wide association studies, as described at http://grants.nih.gov/grants/gwas/ and data sharing policies for other NIH sponsored longitudinal studies. Researchers interested in obtaining controlled-access GuLF data will agree to keep the data secure, use the data only for the approved research purposes, and not to attempt to identify individual study participants. Some data will be made publicly available soon after collection along with information on all data that have been or will be collected. A transparent process for requesting datasets or proposing add-on studies will be established and made available on the study website. In recognition of the rights and intellectual contributions of the

GuLF investigators to publish the data within a reasonable timeframe, outside researchers will also agree to observe a twelve-month moratorium on submitting abstracts and publications using the data. Access to the data will be granted by an NIH Data Access Committee which will ensure that these conditions are met initially and monitor subsequent compliance during the study.

11.4 Study Records Retention

All study records will be retained for at least 5 years after the end of the study. Study records that will be retained include IRB approvals and correspondence, signed informed consent forms, tracking logs, contact information update forms, and other study documentation that may be developed during the course of the study. To protect against accidental or premature destruction of these documents, the records will be maintained in a secure, locked storage areas that are only accessible to study staff.

All study data will be housed in a single data repository. This single database ensures that all system users are accessing the same database; allows for greater control via role-based access privileges; provides a robust architecture to support backup, security, and disaster recovery; and provides the flexibility needed to change the data input mechanisms that could change during a potentially long study.

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Appendix B: Schedule of Procedures/Evaluations

Study Activities	Screening / Enrollment	Home Visit	Year 1	Year 2	Year 3	Year 4
Consent	A, P, B					
Baseline questionnaires	A, P, B	A, B				
Biological samples		A, B	B		B	
Anthropometric measurements		A, B	B		B	
Physiological assessments		A, B	B		B	
Environmental sampling		A, B	B		B	
Test results report		A, B	B		B	
Follow-up questionnaires			B	A, B	B	A, B
Health surveillance			B	A, P, B	B	A, P, B
Contact information update			A, P, B	A, P, B	A, P, B	A, P, B
Newsletter			A, P, B	A, P, B	A, P, B	A, P, B

A = Active Cohort; P = Passive Cohort; B=Biomedical Surveillance Sub-cohort

Appendix C: Lab Processing Flow Sheet/Template for Specimen Collection

In the attached diagrams, we show how the collected biospecimens are processed and packaged in the field for transport to the Central Laboratory (Appendix C1); how personnel at the central laboratory will further process the samples once they have been received (Appendix C2); and how personnel at Environmental Pathology Laboratories (EPL), the NIEHS Repository, will process the received samples prior to placing them into liquid nitrogen (LN2) vapor phase (~-140° C), -80° C mechanical freezers, -20° C walk-in freezers, or into temperature and humidity controlled ambient storage. Note that wherever possible aliquots of the various specimen types are divided into two separate storage locations to ensure that at least part of the sample will survive in the very unlikely event that one storage device should fail catastrophically.

Appendix C1:

This diagram schematically illustrates processing of hair, blood, urine, toenails, dust samples and tap water by the home health agent (HVA) while in the study participant's home.

- Only the two red top blood collection tubes need processing in the field. After clotting for 30 minutes, the HVA will centrifuge the samples for 10-15 minutes at 2500 x g, and removed the serum supernatant into two 5 ml aliquot tubes. The stopper will be replaced on the red top tubes with the residual clots and these are placed into biospecimen bag #1 along with the remaining 6 blood collection tubes (2 lavender, 1 royal blue, 1 yellow, and one PAXgene tube). The 2 ml lavender top tube will be placed in Biospecimen bag #2 for diagnostic testing (CBC with WBC differential) at the central laboratory. Biospecimen Bag #1 is placed in the foam shipper along with a frozen icepack.
- The HVA will use a BD transfer straw to remove 8 ml of urine from the urine collection cup and place it into an 8 ml urine transfer tube. The urine transfer tube will be placed in Biospecimen Bag #3 along with the 2 ml lavender top tube. This sample will be used for the dip stick urinalysis at the central lab. Biospecimen Bag #2 is placed in the foam shipper.
- The remaining urine sample (in the tightly re-sealed original collection cup) is placed into Biospecimen Bag #3. Biospecimen Bag #3 is also placed in the foam shipper. Once all three biospecimen bags are in the foam shipper along with the frozen ice pack the lid is placed on the shipper and it is inserted into the outer cardboard shipping box.
- Hair and nail samples are sealed in labeled manila envelopes and placed on top of the foam shipper lid in the exterior cardboard shipping box.
- The tap water sample will be placed in a Ziploc bag and into the foam shipper
- Dust is collected with a Swiffer™ wipe and placed in the ZipLoc™ bag, which is also placed on top of the foam lid in the outer cardboard box.

The Cardboard shipping box is sealed and either labeled for overnight shipping via FedEx, or the HVA can transport the box to a local Central Laboratory Patient Service Center for further processing and shipping.

Appendix C2.: The Central Laboratory will follow the steps outlined in this appendix.

- ***Biospecimen Bag #1***: The various blood samples in Biospecimen Bag #1 will be processed as shown.
    - Serum will be divided into two sets of five 1 ml aliquots in 1 ml cryovials. Half of the serum aliquots will be placed in freezer storage Box A and the other half in Box B.
    - The two EDTA (lavender top) and one ACD (yellow top) tubes will undergo a discontinuous Percoll gradient separation to isolate the white blood cells (buffy coat) from the plasma and red blood cells (RBC). The EDTA and ACD plasma and RBC fractions will be aliquotted into two different sets of 1 ml cryovials as shown. The EDTA and ADC buffy coat pellets will be stored in separate 1 ml cryovials. The plasma, buffy and RBC aliquots will be divided and half stored in Box A and half in Box B. Boxes A and B will be stored at -80° C in the Central Laboratory until they are shipped to EPL.
    - The two specialty tubes (royal blue-topped trace metals and PAXgene mRNA) are placed in freezer storage Box C along with the two red topped tubes with the red cell clots. Box C will be placed in a -20° C freezer until shipped to EPL.
- ***Biospecimen Bag #2***: The samples in Biospecimen Bag #2 are sent directly to the testing area of the laboratory for analysis. The purple-topped whole blood specimen will be sent to the hematology section where it will undergo a complete blood count (CBC) along with a white blood cell (WBC) differential enumeration. The urine sample will be sent to chemistry for a dipstick urinalysis. The results of both assays will be reported electronically to SRA.
- ***Biospecimen Bag #3***
    - The urine sample from Biospecimen Bag #3 will be aliquotted into four 5 ml aliquot tubes and two tubes will be placed in Box D and two in Box E. These samples will be stored at -80° C until shipped to EPL.
- ***Hair, Nail and Dust Samples***
    - The envelopes containing the hair and nail samples will be placed in a cardboard Box G and stored at ambient temperature until sufficient samples have accumulated to be shipped to EPL
    - Dust samples will be placed in Cardboard Box H until sufficient samples have accumulated to send to EPL.
- ***Tap Water Sample***
    - The tap water will be aliquotted into ten 10 ml screw-capped tubes and placed in Box I and stored at -20° C until shipment to EPL.

Appendix C.3

The top of this diagram illustrates how the Central Laboratory will package the various specimens for shipment to the repository at Environmental Pathology Laboratories.

- ***Foam Shipping Box #1 and Box #2*** will contain the biospecimens contained in Freezer Storage Boxes A and D, plus Boxes B and E respectively. These samples are divided in case one or the other of the boxes is damaged or delayed in shipment to the point that the samples thaw. Both boxes will be packaged with ~10 lbs of dry ice for overnight shipmen to EPL.
- ***Foam Shipping Box #3*** will contain Boxes C, F, and I, which will be transported to EPL on frozen ice packs (not on dry ice).
- ***Cardboard Shipping Box #4*** will contain nail and hair samples. After a sufficient number of these samples have been accumulated, the Central Laboratory will ship these samples to EPL at ambient temperature.
- ***Cardboard Shipping Box #5*** will contain the dust samples. After a sufficient number of these samples have been accumulated, the Central Laboratory will ship these samples to EPL at ambient temperature.

Once shipments have been prepared, the Central Laboratory will send them to EPL via overnight FedEx shipment. Foam Shipping Box #1 and Box #2 will never be sent in the same shipment to preclude total loss of samples from a given set of subjects.

Once the samples have been received at EPL, each frozen sample will have a BSI ID label (Biological Specimen Inventory System, http://www.bsi-ii.com/) cryolabel applied and each sample will be logged into the BSI database. The BSI system will track the exact location of each sample while in storage. The boxes of frozen samples will be stored as shown. Care will be taken so that all samples from one study participant will never be stored in one single storage device.

- Samples from Boxes A, D, B, and E can be stored in LN2 vapor phase or at -80° C in mechanical freezers.
- Samples in Boxes C, F, and I will be stored in EPL's -20° degree walk in freezer.

Hair, nail and dust samples will be stored under ambient conditions in a secure temperature and humidity controlled conditions (~+20° C and 50% humidity) room at EPL.

Appendix D: Informed Consent Form

A health study for oil spill clean-up workers and volunteers

INFORMED CONSENT FORM
For Active Follow-up Study

GuLF Worker Study
Informed Consent Form

Title of Study: Gulf Long-term Follow-up of Clean-up Workers Study

Principal Investigator: Dale P. Sandler, PhD
Epidemiology Branch
National Institute of Environmental Health Sciences

Co-Investigators: Larry Engel, PhD
Epidemiology Service
Memorial Sloan-Kettering Cancer Center

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Associate Investigators Christine Parks, PhD
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1860 Barnett Shoals Rd
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Consent to Participate in a Research Study

You are being asked to be in a research study to evaluate possible short-term and long-term health effects of clean-up activities associated with the recent oil spill in the Gulf of Mexico. The National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health (NIH), Department of Health and Human Services, is leading this research. This study will last at least 10 years. A large group of clean-up workers and a smaller comparison group of people who were not involved in clean-up activities are being asked to enroll in this study. In all, about 55,000 participants will be enrolled in the GuLF Worker Study, with about 27,000 taking part in the active follow-up portion of the study.

Research studies include only people who choose to take part. There will be no bad consequences of choosing not to participate – to your job, finances, health, or otherwise. It is very important that you read and understand the information below. This is called "informed consent." Please take your time making a decision and feel free to discuss it with your friends and family. Before agreeing to take part in this research study, it is important that you read this consent form and understand the answers to any questions you have. You will receive a copy of the form. Please ask the study staff to explain any words or information that you do not clearly understand. When you are done and are satisfied that your questions have been answered, please sign and date the form on the last page if you agree to participate in the study.

What is the purpose of the study?

The purpose of this research study is to learn more about possible short-term and long-term health effects of the recent oil spill in the Gulf of Mexico. We are studying clean-up workers and a small comparison group of people who were not involved in clean-up activities. Much can be learned about the effects of exposure to oil and chemicals used to clean up oil by comparing the health status of those who were involved in clean-up activities and those who were not. We will also study factors among clean-up workers that may explain why some experience health problems and others do not. Because some of the clean-up workers live in the areas most directly affected by the oil spill and others live further away, this study will also allow us to learn how stress and job loss associated with the oil spill can affect health, including mental health.

What if I decide not to participate?

You may decide to participate in this study or not. You may decide to drop out at any time. Your decision will not affect the care you receive from any medical care provider for which you are entitled. If you decide to withdraw from the study at a later date, we will keep the information we have collected up to that point, but will not ask you for any more information. We will continue to use the data and specimens you provided up to the time that we receive a written request from you

asking us not to do so. If you decide to withdraw from the study, you should call 1-855-NIH-GULF (855-644-4853) to tell the study staff your decision. The investigators conducting the study may also decide to withdraw you from the study without your consent if it is later determined that you are not actually eligible or are no longer able to complete the requirements of the study.

Who is conducting the study?

NIEHS designed, conducts, and has overall responsibility for the study. SRA International, a professional services research firm, and their subcontractors are responsible for day-to-day study management. All of these research partners are following guidelines and procedures established by the NIEHS and approved by the NIH Office of Human Subjects Research, which exists to protect persons who participate in research studies.

Who is eligible for the study?

You are eligible to be in this active follow-up portion of the study if you are at least 18 year of age, completed the GuLF Worker Study enrollment questionnaire and meet one or more of the criteria below:

- You were involved with oil spill clean-up activities for at least 1 day, including paid or volunteer work;
- Completed an oil spill training module;
- You were not involved in oil spill clean-up activities, but are similar to persons who were involved in clean-up activities ;
- You resided in one of five states (LA, AL, MS, FL, TX) at the time of the oil spill;
- Or, if you did not reside in one of those five states, you participated in clean-up activities as part of a Federal Civilian or Military job (e.g. OSHA or Coast Guard) or were involved in activities that had the greatest likelihood of exposure to crude or burning oil or chemical dispersants.

What will I be asked to do?

If you agree to be in the study, you will be asked to complete the 4 tasks listed below.

1. Allow our staff to meet with you in your home for 2.5 hours to complete the following study activities:

Complete a health interview

The interview takes about 1 hour to complete. We will ask you questions about your participation in oil spill clean-up activities, your health and lifestyle, personal and family medical history, and places you have lived and worked.

Provide blood, hair, toenail, urine, and saliva samples

- A member of our staff with training and experience in blood collection will collect 3.5 tablespoons of blood from a vein in your arm. Depending on the timing of your appointment, you may be asked to provide this sample before you eat breakfast in the morning.
- You will be asked to provide a few strands of hair (as close to your scalp as possible) and collect small nail clippings from your toes with a toenail clipper.
- You will be asked to provide a first morning urine sample in a small collection cup. You will receive a urine collection kit in the mail before the visit.
- You may also be asked to provide a saliva (spit) sample.

Undergo a physical examination

During the home visit, you will be asked to undergo a brief physical examination. Our staff will measure your height, weight, and blood pressure. Your hip and waist circumference will be measured over your clothes. These procedures take about 10 minutes to complete.

You may be asked to complete a lung function test. This test will require you to take a deep breath and exhale forcefully into a hand-held device that measure your lung function (spirometer). You will be asked repeat this process several times. The lung function test takes about 5 to 10 minutes to complete.

Allow our staff to collect environmental samples from your home

Our staff will use a dust wipe to collect dust samples from your living room, bedroom, and kitchen. The procedure will take 5 to 10 minutes to complete.

Our staff will also collect a sample of water from the tap at your kitchen sink. This procedure takes about 5 minutes to complete.

2. Provide us with updated contact information once a year.

We will send you a contact information update form once a year along with a study newsletter. We would like you to complete and return the form, even if there is no change in your contact information. You will be given extra copies of the update form so that you can share updates with us as soon as they occur.

3. Complete a 30-minute telephone questionnaire every 2 years.

After the initial home visit, we will contact you by phone every 2 years and ask you to complete a questionnaire. The purpose of the questionnaire is to collect updated information about your health and lifestyle.

4. Allow us to contact you about participation in more detailed health studies.

After the initial home visit, we will select a smaller group of participants to participate in more detailed medical examinations. These will include more complete lung function testing, tests of neurological function (e.g. memory loss, performance on timed tests) and collection of additional blood and household samples such as dust collected with a vacuum cleaner. If you are selected, you will be given a chance to agree or not agree to participate in this additional part of the study at that time.

5. Allow us to passively monitor your health outcomes.

After the initial home visit, we will monitor the occurrence of any health outcomes that you experience through existing state and national surveillance systems. These health outcomes include diagnoses such as a heart attack, stroke, asthma, mental disorders, and death. Diagnoses from hospital visits and Medicare and Medicaid claims would also be monitored.

How long will my participation last?

Participants in this study will be followed for at least 10 years. The information that we collect becomes more valuable over time as participants experience changes in their health. These changes will help us better understand any possible long-term health impacts of the Gulf of Mexico oil spill. The duration of the study may be extended beyond 10 years, depending on what we learn early on. We hope that you will participate for the full length of the study. However, participation is completely voluntary, and you are free to withdraw from the study at any time.

Will information I provide be shared with others?

If you decide to participate in the study, we may share your name and contact information with other researchers who want to conduct additional studies related to the oil spill. These researchers may contact you in the future and invite you to take part in other studies. Your participation will be entirely voluntary. The purpose of any additional research will be explained to you so that you can decide whether or not you would like to participate. All of the studies will be required to meet standards set by GuLF study investigators for demonstrating scientific validity and protecting your rights and privacy.

Information that cannot identify you may be made available for others to analyze through information that is posted on the GuLF Workers Study Website or by special request. The website may include summary tables and provide a mechanism for researchers to request information about specific individuals but

without your name and identifying information attached. Your identifying information will be kept confidential but it may be shared for specific research studies as described above.

How will my study information be used?

The information and samples that you and other participants provide will be analyzed to better understand the short-term and long-term health effects that may occur from the oil spill among clean-up workers and community members. The combined results for all participants will be used to prepare reports and summaries for scientific publications and scientific meetings. The findings from the study may influence long-term public health responses in Gulf communities or responses to similar disasters that may occur in the future. The study is not intended to diagnose and treat illness that individuals may experience as a result of the oil spill.

We will use the identifying information you shared (but not the questionnaire or health data) to link to vital records (such as death certificates) and State cancer Registries so that we can track the incidence of cancer and mortality among study participants. We may also link a list of study participants to other electronic health records that become available during the years of the study to obtain information on the frequency of specific newly developed medical conditions among study participants.

Will I receive any test results?

You will receive results from some laboratory tests and study procedures. The results will be shared in the form of a report. The report will provide you with your results, normal ranges for each result, and an explanation of what each test result may mean. The tests we do are for research purposes and should not be considered a medical diagnosis. We will let you know whether we think you should see a doctor based on the results. If you do not have a regular doctor, you may call the study center (1-800-123-4567) to receive a referral to a local health care provider. We will not provide medical care as part of this study. The results will not be shared with your employer or health insurance provider. Scientific reports from the study can be accessed and viewed on the GuLF Worker Study website.

How will my specimens be used?

All of the samples that you provide will be frozen and stored indefinitely in a secure laboratory. At a later date, we will analyze your samples for research purposes. We will look for signs of oil exposure and related health effects. We will test your samples for a variety of chemicals, hormones, and environmental agents. We will also use the samples to study effects on genes and study whether specific genetic factors interact with chemical exposures to increase or

decrease the likelihood of any health effects related to the oil spill. All research tests will not be done on all participants. We will not test for illegal drugs.

At this time, the exact number and specific types of tests that we will perform on samples have not been determined. Although the analysis of your samples for research purposes may reveal clinically relevant information, it may be many years before your samples are analyzed. Furthermore, the tests we do for research purposes may not be done in a certified clinical laboratory. Therefore, you should continue to visit your doctor for routine health care. In the event we discover something that could be clinically relevant, we will work with our Institutional Review Board to develop an appropriate plan for informing you. Options include letting you or your doctor know about your specific test results, informing all participants of general findings so that you may inform your doctor who may want to do further tests, or not informing you when others agree that it is not clearly of clinical value.

How will my confidentiality be protected?

Every effort will be made to protect your confidentiality. All of your samples, the questionnaires, and other study documents will be labeled with a special identification number, rather than your name. All study materials will be stored in either locked storage areas or on secured computers.

Records that identify you in this study are private. No one other than research staff can look at them unless you agree to it. This is because the study has been granted a Certificate of Confidentiality under a federal law [Section 301(d) of the Public Health Service Act]. The Certificate helps researchers protect the privacy of research participants. With a Certificate of Confidentiality, researchers cannot be forced by anyone to give information that could identify you.

A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about a participant if is considered necessary to protect the participant or someone else from harm. You should be aware that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer or employers learns about your participation from you and you consent in writing to having the information released, then we cannot use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

What are the benefits of participating?

You will not receive any direct health benefits from participating in the study. However, you may feel a sense of pride in taking part in a study that will help answer questions about the potential short-term and long-term health impacts of the Gulf of Mexico oil spill. You may also benefit from receiving the results of blood and urine tests and referrals for health care that you may not have

otherwise received. By participating in this study you may be helping your community and others by helping researchers understand what to expect following an oil spill.

What are the risks of participating?

This study involves very minimal risk to participants.

The interview and telephone survey contain questions that may make you feel uncomfortable. You may refuse to answer any questions. You may also end the interview at any time.

There is a small risk of bruising or infection at the spot where the blood sample is drawn. Signs of infection are swelling, redness, and tenderness. The lung function test may cause coughing and a feeling of lightheadedness. These symptoms usually go away immediately after testing. If you have signs of infection or continue to experience coughing or lightheadedness after the home visit, please contact your doctor or call the GuLF study staff at 1-800-123-4567.

There is a slight risk of accidental breach of confidentiality. We will do everything we can to see that this does not happen. The study has a Certificate of Confidentiality so that we cannot be forced to give out information that could identify you. The steps that we will take to maintain your confidentiality are described above – see “How will my confidentiality be protected?”

Are there any costs for participating in this study?

There are no costs to you other than the time and effort required to complete study activities. Costs for the home visit, telephone questionnaire, and other study activities will be paid by the study.

Will I receive compensation for my time and effort?

You will receive a $25 dollar gift card for completing the home visit and $10 dollar gift card for completing each of the telephone questionnaires. The total level of compensation for the first 10 years of the study is equivalent to $65. You will receive your gift cards by mail within 2 to 3 weeks of completing each study event.

Who should I contact for more information about the study?

You have the right to ask questions about the study and to receive answers about your questions. You are encouraged to ask questions about the study before you decide to participate and any time during the study.

During the home visit, our study staff will answer questions for you. After the home visit, you may call the toll-free number for the study center at 1-855-NIH-GULF (1-855-644-4853) and ask to speak to either a member of the study staff

or the principal investigator, Dr. Dale Sandler. If you have questions about your rights as a research participant, please contact the NIEHS Institutional Review Board at 1-919-541-3852.

Participant Statement

I have read the consent form and received a copy for my records. I received answers to my questions about the study. I understand the requirements, risks, and benefits of the study. I understand that participation is voluntary and that I may withdraw from the study at any time. I understand that by agreeing to participate in the study, I do waive any rights regarding access to and disclosure of my records.

Signature of Participant	Date
Printed Name of Participant	
Signature of Witness	Date
Printed Name of Witness	

Appendix E: Lead Letter

GuLF Worker Study

A health study for oil spill clean-up workers and volunteers

Participant Name
Participant Address 1
Participant Address 2
Participant City, State, ZIP

Date

Dear [Participant Name]:

In a couple of weeks, you will receive a call inviting you to participate in a research study on the potential short-term and long-term health effects associated with oil spill clean-up activities in the Gulf of Mexico. The National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health (NIH), is leading this research effort.

We are studying clean-up workers (including paid workers and volunteers) and a smaller group of people who were not involved in clean-up activities. Much can be learned by comparing the health status of those who were involved in clean-up activities to those who were not. We will also study factors among clean-up workers that may explain why some experience health conditions while others do not. The study will also explore health concerns related to other factors associated with the oil spill, such as loss of income, worries about the future, and potential residential exposure to chemicals from the oil spill. In all, about 55,000 participants will be enrolled into the study.

You have been selected to participate in this study from rosters of persons involved in oil-spill clean-up or receiving clean-up related safety training. You will be contacted by a study representative by telephone to learn more about this important health study and have an opportunity to participate.

During the call, the study representative will need about 30 minutes of your time for a voluntary survey to ask about your clean-up activities, if any, and about your health and well-being during this time. After completion of this survey, we will use identifying information that you share to link with national, state and local records, like death certificates and cancer registries, to follow any health outcomes you experience over the next 10 or more years. Additionally, you may be asked to actively continue with the study by allowing us to send an examiner to your home to make some clinical measurements (like height and weight) and obtain clinical samples (like blood and urine) and environmental samples (like house dust). Agreeing to the telephone interview does not obligate you to participate in the home visit. You will be given the opportunity to learn more about being a study participant and have a chance to agree or not agree to participate. If you are selected and choose to actively participate, you will receive a gift card worth $25 for completing the next step and will be eligible for additional compensation in future years.

The information collected by this study is confidential and will only be used for research and analysis and cannot be used for any other purposes.

Your help is extremely important to the success of this study and the understanding of any potential health effects associated with oil clean-up work. If you would like to learn more about the study, please visit http://www.gulfworkerstudy.org or call 1-855-NIH-GULF (1-855-644-4853). We look forward to talking with you and thank you in advance for your cooperation.

Sincerely Yours,

NIEHS Principal Investigator

SRA Project Director

Appendix F: Brochure

GuLF Worker Study

A health study for oil spill clean-up workers and volunteers

What is the GuLF Worker Study?

The Gulf Worker Study is examining the potential short-term and long-term health effects of clean-up activities associated with the recent oil spill in the Gulf of Mexico. The National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health (NIH), is leading this research effort.

NIEHS is studying clean-up workers and a small comparison group of people who were not involved in clean-up activities. In all, about 55,000 participants will be enrolled into the GuLF Worker Study.

The study will compare the health status of those who were involved in clean-up activities to those who were not. In addition, this study will provide valuable information about how stress and job loss associated with the oil spill can affect health, including mental health.

Who is eligible?

You are eligible if you are at least 18 years of age and meet one or more of the criteria below:

- You were involved with oil spill clean-up activities for at least 1 day, including paid or volunteer work;
- Completed an oil spill training module;
- You were not involved in oil spill clean-up activities, but are similar to persons who were involved in clean-up work;
- You resided in one of five states (LA, AL, MS, FL, TX) at the time of the oil spill OR you live in another state, but participated in clean-up activities as part of a Federal Civilian or Military job or were involved in activities involving exposure to crude or burning oil or chemical dispersants.

What will I be asked to do?

You will be asked to complete a 30 minute telephone enrollment questionnaire, which includes questions about your participation in oil spill clean-up activities, your health and lifestyle, and places you have lived and worked. We will use identifying information that you share to link with national, state and local records, like death certificates and cancer registries, to follow the cancer incidence, morbidity and mortality among oil spill workers over the next 10 or more years. Each year, we will send you a study newsletter and ask you to update your contact information.

Some participants will be invited to take part in the active follow-up phase of this study. This phase of the study involves a home visit. During the visit, you will be asked to complete an interview and provide some biologic samples (e.g. blood, hair, toenails) and environmental samples (e.g. tap water and dust) from your home. After the home visit, we will ask you to complete a telephone questionnaire every two years.

A smaller group of participants may be invited to take part in additional medical evaluations, such as additional blood tests, complete lung function testing, and tests of memory.

Participation is completely voluntary

Why should I participate?

This is the largest and most comprehensive study that has ever been conducted on the health effects of an oil spill. By taking part in this study, you will be helping your community and others by helping researchers understand the health impacts related to an oil spill.

How will my confidentiality be protected?

Every effort will be made to protect your confidentiality. Records that identify you in this study are private. No one other than research staff can look at them unless you agree to it. This is because the study has been granted a Certificate of Confidentiality. With a Certificate of Confidentiality, researchers cannot be forced by anyone to give information that could identify you at any point in time.

How can I find out more?

To find out more information about the GuLF Worker Study, call toll free 1-855-NIH-GULF (1-855-644-4853) between 9 AM and 9 PM Monday through Saturday and 12 PM to 6 PM on Sunday. You may also visit www.gulfworkerstudy.com.

Thank you for your participation.

NIEHS National Institute of Environmental Health Sciences

Appendix G: Frequently Asked Questions

Appendix H: Enrollment Questionnaires

Appendix I: Baseline Questionnaires